CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212379Orig1s000

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)	212379
Priority or Standard	Standard
Submit Date(s)	12-20-2018
Received Date(s)	12-20-2018
PDUFA Goal Date	10-20-2019
Division/Office	Division of Dermatology and Dental Products
Review Completion Date	10-17-2019
Established/Proper Name	minocycline topical foam, 4%
(Proposed) Trade Name	AMZEEQ
Pharmacologic Class	Acne Agents
Code Name	FMX-101
Applicant	Foamix Pharmaceuticals Inc.
Dosage Form	foam
Applicant Proposed Dosing Regimen	Apply to affected areas once daily
Applicant Proposed Indication(s)/Population(s)	For the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	Acne vulgaris (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	AMZEEQ is a tetracycline-class drug indicated to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	88616000 |Acne vulgaris (disorder)|
Recommended Dosing Regimen	Apply AMZEEQ to affected areas once daily. AMZEEQ should be gently rubbed into the skin.

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jennifer Harmon
Nonclinical Reviewer	Renqin Duan
Nonclinical Supervisor	Barbara Hill
Office of Clinical Pharmacology Reviewer(s)	Sojeong Yi
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Kevin Clark/Patricia Brown
Clinical Team Leader	Gordana Diglisic
Statistical Reviewer	Matthew Guerra
Statistical Team Leader	Mohamed Alosh
Cross-Disciplinary Team Leader	Gordana Diglisic
Acting Associate Director for Labeling	Nancy Xu
Division Director (OB)	Laura Lee Johnson
Division Director	Kendall Marcus

Additional Reviewers of Application

OPQ	Application Technical Lead: Hamid Shafiei Regulatory Business Process Manager: Bamidele (Florence) Aisida Drug Substance: Joseph Leginus/Donna Christner Drug Product: Hailin (Sheena) Wang/Moo-Jhong Rhee Manufacturing: Youmin Wang/Yubing Tang Biopharmaceutics: Kalpana Paudel/Vidula Kolhatkar Microbiology: Julia Marre/ Denise Miller
OPDP	Laurie Buonaccorsi/Matthew Falter
OSI	Cheryl Grandinetti/Phillip Kronstein
OSE/DEPI	Tri Bui Nguyen/Vicky Chan
OSE/DMEPA	Madhuri Patel/Teresa McMillan
DPMH	Jane Liedtka/Denise Pica-Branco/Miriam Dinatale/Ramy Abdelrahman/Mona Khurana
Patient Labeling	Susan Redwood/Barbara Fuller

OB = Office of Bioequivalance
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Office of Pharmaceutical Quality Supervisor	Hammid Shafiei, PhD			Select one: _X__ Authored _X__ Approved
	Signature: See DAARTS			
Nonclinical Reviewer	Renqin Duan, PhD	OND/ODE 3/DDDP	Sections: 5, 19.3	Select one: _X__ Authored ___ Approved
	Signature: See DAARTS			
Nonclinical Supervisor	Barbara Hill, PhD	OND/ODE 3/DDDP	Sections: 5, 19.3	Select one: ___ Authored _X__ Approved
	Signature: See DAARTS			
Clinical Pharmacology Reviewer	Sojeong Yi, PhD	DCP-III/OCP/OTS/CDER	Sections 6, 11.1, 19.4	Select one: __X_ Authored ___ Approved
	Signature: See DAARTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	DCP-III/OCP/OTS/CDER	Sections 6, 11.1, 19.4	Select one: _X_ Authored _X_ Approved
	Signature: See DAARTS			
Statistical Reviewer	Matthew Guerra, PhD	OTS/OB/DBIII	Sections: 7.2, 8.1, 8.3, and 8.4	Select one: _X_ Authored ___ Approved
	Signature: See DAARTS			
Statistical Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 7.2, 8.1, 8.3, and 8.4	Select one: ___ Authored _X_ Approved
	Signature: See DAARTS			
Division Director (OB)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections: 7.2, 8.1, 8.3, and 8.4	Select one: ___ Authored _ X _ Approved
	Signature: See DAARTS			
Clinical Reviewer	Patricia Brown, MD	OND/ODEIII/DDDP	Sections: 1, 2, 3, 4.1, 4.3, 4.4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.5	Select one: _X_ Authored ___ Approved
	Signature: See DAARTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Kevin Clark, MD	OND/ODEIII/DDDP	Sections: 1, 2, 3, 4.1, 4.3, 4.4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.5	Select one: _X_ Authored ___ Approved
	Signature: See DAARTS			
Clinical Team Leader	Gordana Diglisic, MD	OND/ODEIII/DDDP	Sections: 1, 2, 3, 4.1, 4.3, 4.4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.5	Select one: ___ Authored _X_ Approved
	Signature: See DAARTS			
Division Director (Clinical)	Kendall Marcus, MD	OND/ODEIII/DDDP	Sections: All	Select one: ___ Authored _X__ Approved
	Signature: See DAARTS			

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
AV	acne vulgaris
AUC_{0-24}	area under the 24-hour concentration time-curve
BLA	biologics license application
CFR	Code of Federal Regulations
CNS	central nervous system
CPK	creatine phosphokinase
DHOT	Division of Hematology Oncology Toxicology
DMF	drug master file
ECG	electrocardiogram
EOP2	end-of-Phase 2
FDA	Food and Drug Administration
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
iPSP	initial Pediatric Study Plan
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD	listed drug
MI	multiple imputation
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no-observed-adverse-effect-level
OCP	Office of Clinical Pharmacology
OECD	Organization for Economic Co-operation and Development
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRO	patient-reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system-organ class
TEAE	treatment-emergent adverse event

TEAR	treatment-emergent adverse reaction
UPT	urine pregnancy test
URI	upper respiratory infection
URTI	upper respiratory tract infection

1. Executive Summary

1.1. Product Introduction

The Applicant is seeking approval for AMZEEQ™ (minocycline) topical foam, 4% 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, 4% 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, as well as intravenous (IV) injection. There are no topical formulations of minocycline currently marketed in the United States. The proposed indication is the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. The proposed dosing regimen is application to the affected areas once daily.

The Agency concluded that the proposed proprietary name, AMZEEQ™, was acceptable from both a promotional and safety perspective under NDA 212379 (Proprietary Name Review by Dr. Madhuri Patel, Division of Medication Error Prevention and Analysis dated March 12, 2019).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from three adequate and well-controlled trials (FX2014-04, FX2014-05, and FX2017-22) which provided evidence of the effectiveness of minocycline foam, 4% for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in the target population. All three trials assessed the changes from baseline to Week 12 for the following co-primary endpoints:

- Absolute change in the inflammatory lesion count
- Proportion of subjects with treatment success, defined as an Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 (''almost clear") and at least a two-grade improvement (decrease) from baseline

Minocycline foam, 4% was statistically superior to vehicle (p-values ≤0.039) on the co-primary endpoints in Trials FX2014-05 and FX2017-22. In Trial FX2014-04, minocycline foam, 4% was statistically superior to vehicle on absolute change in inflammatory lesion counts, but not for treatment success on the IGA scale. The Applicant has demonstrated that minocycline foam, 4% 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.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Foamix Pharmaceuticals submitted a new drug application (NDA) 212379 for AMZEEQ™ (minocycline) topical foam, 4% under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication is the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. AMZEEQ™ is a new dosage form of minocycline and the safety profile of the moiety is well characterized. The listed drug (LD) is SOLODYN®(minocycline hydrochloride) Extended Release Tablets (NDA 50808). The Applicant established a clinical bridge between minocycline foam, 4% 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 of three 12-week, multicenter, randomized, double-blind, vehicle-controlled trials enrolling 2,418 subjects ages 9 years and older with moderate to severe acne vulgaris, minocycline foam, 4% was statistically superior to vehicle for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. The co-primary efficacy endpoints were the absolute change from baseline in inflammatory lesion counts at Week 12 and the proportion of subjects with 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, 4% was adequately characterized during the drug development program. There were no deaths or drug-related serious adverse events (SAEs) in the Phase 3 trials FX2014-04, FX2014-05, and FX2017-22 (the Phase 3 Primary Pool). In the Phase 3 Primary Pool, SAEs occurred in 0.4% of subjects in the minocycline foam, 4% group and in 0.5% of subjects in the vehicle group. Active assessments of local tolerability in the Phase 3 Primary Pool revealed the following results at Week 12: erythema (15.7%), hyperpigmentation (15.3%), dryness (7.4%), itching (6.0%), and peeling (3.4%). Investigators characterized the hyperpigmentation as being characteristic of inflammatory and postinflammatory changes associated with acne. Most local tolerability signs and symptoms were mild in severity and occurred with similar frequency compared with subjects treated with the vehicle component of minocycline foam, 4%. The most common adverse reaction (AR) was headache, which was reported in 3% of subjects treated with minocycline foam, 4% and 2% of subjects treated with vehicle. The Applicant also submitted long-term safety data from an additional 40 weeks of treatment in two of the Phase 3 trials.

Although systemic exposure from topical administration of minocycline foam, 4% 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 minocycline foam, 4%.

In summary, acne vulgaris is a chronic disease which may be associated with substantial impairment of quality of life. Minocycline foam, 4% provides an additional treatment option. The available evidence of safety and efficacy supports the approval of AMZEEQ™ (minocycline) topical foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 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	Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles and primarily affects adolescents and young adults. Acne occurs most frequently on the face and is characterized by two major types of lesions: noninflammatory (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules). The etiology is multifactorial. Acne may be associated with substantial impairment of quality of life because of the chronic relapsing and remitting course and potential for scarring after lesions resolve.	Acne is a common chronic disorder with a range of disease severities which may significantly impact quality of life.
Current Treatment Options	Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g., sarecycline, erythromycin, clindamycin, benzoyl peroxide) systemic hormonal therapies (e.g., ethinyl estradiol/norgestimate) and topical retinoids (e.g., tretinoin, tazarotene). Oral formulations of isotretinoin are available for severe, recalcitrant, nodulo-cystic acne.	There are a number of FDA-approved products with an acceptable benefit/risk profile for the treatment of acne vulgaris in adolescents and adults. Minocycline, when administered orally, is effective for the treatment of inflammatory lesions of acne vulgaris. A topical formulation of minocycline effective in the treatment of inflammatory lesions of acne vulgaris with less systemic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options (continued)	Treatment is individualized according to the types of lesions, severity of disease, and patient preferences.	exposure than oral minocycline would be a useful addition to the treatment armamentarium.
Benefit	Data from two of three adequate and well-controlled trials provide substantial evidence of the effectiveness of minocycline foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. These trials enrolled 2,418 subjects ages 9 years and older with moderate to severe acne vulgaris. Minocycline foam, 4% was statistically superior to vehicle for the co-primary efficacy endpoints of absolute change from baseline in inflammatory lesion counts at Week 12 and the proportion of subjects with 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 this new dosage form and route of administration for minocycline. Minocycline foam, 4% was well tolerated in all evaluated subgroups.	Minocycline foam, 4% provides an effective and safe treatment option for inflammatory lesions of moderate to severe acne vulgaris.
Risk and Risk Management	The primary safety database (Trials FX2014-04, FX2014-05, and FX2017-22) included 1,356 subjects who were treated with minocycline foam, 4%. There were no deaths or treatment-related serious adverse events. The most common adverse reaction (AR) was headache, which was reported in 3% of subjects treated with minocycline foam, 4% and 2% of subjects treated with vehicle. Local tolerability signs and symptoms at Week 12 included: erythema (15.7%), hyperpigmentation (15.3%), dryness (7.4%), itching (6.0%), and peeling (3.4%). Investigators characterized the hyperpigmentation as being characteristic of inflammatory and postinflammatory changes associated with acne. Most local tolerability signs and symptoms were mild in severity and occurred with similar frequency compared with subjects treated with the vehicle component of minocycline foam, 4%.	The risks associated with use of minocycline foam, 4% are favorable in comparison to oral minocycline products. Most subjects had no local reactions and those that occurred were mostly mild in severity. Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Ris and Risk Management (continued)	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.	

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application

☐	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)	Section 8.2.6
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.1
		☐	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 were not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Acne vulgaris is a common, chronic dermatological disorder. In the United States, acne affects more than 50 million individuals.[1] The highest prevalence is among adolescents and young adults; however, acne may occur in children and adults at any age. Among adults with acne, females are more commonly affected than males.[2,3]

Acne is an inflammatory disease of sebaceous follicles. Factors which contribute to the complex pathophysiology of acne include bacterial colonization of follicles, hypersecretion of the sebaceous glands, and intrafollicular hypercornification. At adrenarche, increased androgen stimulation may result in both abnormal keratinization of the sebaceous follicle and increased sebum production in the sebaceous gland. Obstruction of the follicular orifice of the sebaceous gland by desquamated keratinocytes produces a microcomedone. Prolonged fundibular blockage, proliferation of propionibacterium acnes in the sebaceous follicle, and production of multiple chemoattractant and proinflammatory cytokines may trigger the formation of noninflammatory and inflammatory lesions.[4]

Acne may present with a variety of lesions which may be categorized as one of the following types:

1. Noninflammatory: Noninflammatory lesions include the open comedones (blackheads) or closed comedones (whiteheads).
2. Inflammatory: Inflammatory lesions include papules, pustules, nodules, and cysts.

Both lesion types develop from microcomedones[5] and most frequently occur on the face. However, lesions may be localized to other areas with a high density of sebaceous follicles such as the neck, chest, and back. Factors which may influence the risk or presentation of acne are age, sex, and genetic predisposition. Variants of acne which may require more aggressive or specialized treatment include acne fulminans, acne conglobate, synovitis/acne/pustulosis/hyperostosis/osteitis syndrome, pyogenic arthritis/pyoderma gangrenosum/acne syndrome, neonatal acne, and acne complicated by gram-negative folliculitis.

The clinical course is characterized by remissions and recurrences. In some individuals, acne may persist for decades and resolve with scarring. The association of acne with depression,

[1] Bhate K, Williams HC. Epidemiology of acne vulgaris. BJD. 2013 168, pp474–485.
[2] UpToDate. Thiboutot, D et al. Accessed May 9, 2018.
[3] Zaenglein AL et al. Guidelines of care for the management of acne vulgaris. JAAD. 2016 May;74(5):945-73.e33
[4] Brown SK, Shalita AR. Acne vulgaris. Lancet. 1998. 351; 9119:1871-1876.
[5] Dawson AL et al. Acne Vulgaris. BMJ 2013;346: 2634

anxiety, and reduced quality of life is well documented.[6] Successful treatment may produce a significant improvement in self-esteem.[7]

2.2. Analysis of Current Treatment Options

The treatment armamentarium for acne vulgaris includes both topical and systemic products. Treatments target one or more of the primary pathogenic factors: sebaceous gland hypersecretion stimulated by androgen production, bacterial proliferation, and abnormal keratinization with resultant follicular obstruction and inflammation.

Most of the FDA-approved therapies belong to the following pharmacologic classes: antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide, dapsone), hormonal agents (e.g., ethinyl estradiol/norgestimate), and retinoids (e.g., tretinoin, tazarotene, isotretinoin). Other treatment options which are used less frequently include: physical modalities (e.g., chemical peels, intralesional corticosteroids and laser therapy), complementary/alternative therapies (e.g., tea tree oil, herbal supplements and biofeedback), and dietary management (e.g., low-glycemic index diets and low-calcium diets). Factors which influence the choice of treatment are lesion type(s), disease severity, personal preference, and individual patient characteristics (e.g., age, sex, skin sensitivity, predisposition for hyperpigmentation/scarring). Topical products such as benzoyl peroxide, retinoids, and antibiotics are indicated for acne of mild to moderate severity;8 whereas, oral sarecycline is indicated for moderate to severe acne and oral formulations of isotretinoin are indicated for severe, recalcitrant, nodulo-cystic acne. Topical products may contain a single active ingredient or two active ingredients which may address different lesion types.

Categories of drug products and examples of topical and systemic therapies currently approved for the treatment of acne vulgaris are presented in Table 1 , Table 2, and Table 3 below.

[6] Lasek RJ et al. Acne Vulgaris and the Quality of Life of Adult Dermatology Patients. Arch Dernmatol.1998; 134(4): 454-458.
[7] Newton JN et al. The effectiveness of acne treatment: an assessment by patients of the outcome of therapy. Br J Dermatol. 1997;137(4):563
[8] Zaenglein AL, et al. Guidelines of care for the management of acne vulgaris. JAAD.2016:75:945-73

Table 1: Categories of Drug Products for Acne Treatment

Categories	Drug Products
Topical	
Benzoyl peroxide[1]	Multiple products
Sulfa products	Sulfacetamide, sulfacetamide/sulfur
Azelaic acid	Azelaic acid cream
Antibiotics	Clindamycin, erythromycin, dapsone
Retinoids	Tretinoin, adapalene, tazarotene
Salicylic acid[1]	Multiple products
Systemic	
Antibiotics[2]	Tetracycline, doxycycline, minocycline, sarecycline
Retinoids isotretinoin	Isotretinoin
Hormonal therapies[3]	Various oral contraceptives

Source: Modified from NDA 209269, Clinical Review by Patricia Brown, MD
[1] Over-the counter monograph approved products
[2] Azithromycin/erythromycin, Ampicillin/amoxicillin used off- label
[3] Spironolactone, flutamide, corticosteroids used off- label

Table 2: Representative Examples of FDA-Approved Topical Products

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Antimicrobials				
ACZONE (dapsone) gel, 7.5%, NDA 207154 (2016)	Topical treatment of acne vulgaris in patients 12 years of age and older	Apply a pea-sized amount in a thin layer to the entire face once daily	2, 12-week R, DB, VC trials in 4,340 subjects Active vs. vehicle 1.GAAS: 30% vs. 21% Inflam: 56% vs. 49% Noninflam: 45% vs. 39% -2.GAAS: 30% vs. 21% Inflam: 54% vs. 48% Noninflam: 46% vs. 41%	AR: application site dryness and pruritus W&P: methemoglobinemia, hemolysis, peripheral neuropathy, skin reactions
EVOCLIN® (clindamycin phosphate) foam, 1% NDA 050801 (2004)	Acne vulgaris in patients 12 years and older	Apply once- daily to affected areas	A 12-week R, DB, VC trial in 513 subjects with mild to moderate acne. active vs. vehicle IGSA: 31% vs. 18% Inflam:49% vs. 35% Noninflam: 38% vs. 27%	AR: headache, application site burning, application site pruritus, application site dryness, application site reactions W&P: colitis, irritation
AZELEX® (azelaic acid cream) 20% NDA 020428 (1995)	Topical treatment of mild- to-moderate inflammatory acne vulgaris	Apply a thin film to affected areas twice daily	Not included	AR: pruritus, burning, stinging and tingling W&P: hypopigmentation, sensitivity or irritation

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Retinoids				
ALTRENO™ (tretinoin) lotion, 0.05% NDA 209353 (2018)	Topical treatment of acne vulgaris in patients 9 years of age or older	Apply once- daily to the affected areas	2, 12-week R, DB, VC trials in 1,640 subjects 9 years and older with moderate to severe acne vulgaris active vs. vehicle 1.EGSS: 17% vs. 7% Inflam: 51% vs. 40% Noninflam: 48% vs. 27% 2.EGSS: 19% vs. 13% Inflam: 53% vs. 42% Noninflam: 46% vs. 32%	AR: application site dryness, pain, erythema, irritation, exfoliation W&P: skin irritation, ultraviolet light and environmental exposure (minimize exposure), fish allergies (caution if allergic to fish)
FABIOR™ (tazarotene) foam, 0.1% NDA 202428 (2012)	Topical treatment of acne vulgaris in patients 12 years of age or older	Apply once- daily in the evening after washing with a mild cleanser and fully drying the affected area	2, 12-week R, DB, VC trials in 1,485 subjects 12 years and older with moderate to severe acne vulgaris active vs. vehicle 1.IGA: 29% vs. 16% Inflam: 58% vs. 45% Noninflam: 55% vs. 33% Total: 56% vs. 39% -2.IGA: 28% vs. 13% Inflam: 57% vs. 41% Noninflam: 46% vs. 41% Total: 56% vs. 43%	AR: application site irritation, dryness, erythema, exfoliation, pain, photosensitivity, pruritus, dermatitis W&P: fetal risk, local irritation, irritant effect with concomitant topical medications, photosensitivity and risk for sunburn, flammability
DIFFERIN® (adapalene) lotion 0.1% NDA 022502 (2010)	Topical treatment of acne vulgaris in patients 12 years and older	Apply a thin film to the entire face and other affected areas of the skin once daily, after washing gently with a mild soap less cleanser	2, 12-week R, DB, VC trials in 2,141 subjects active vs. vehicle 1.IGA: 26% vs. 17% Inflam: 55% vs. 40% Noninflam: 50% vs. 36% Total: 52% vs. 37% -2.IGA: 24% vs. 16% Inflam: 46% vs. 37% Noninflam: 43% vs. 30% Total: 45% vs. 33%	AR: dry skin, skin irritation, skin burning/skin discomfort, sunburn W&P: UV light and environmental exposure, local cutaneous reactions

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Combination Products				
ACANYA™ gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) NDA 050819 (2008)	Topical treatment of acne vulgaris in patients 12 years or older.	Apply a pea-sized amount of ACANYA Gel to the face once daily	2, 12-week R, DB, VC trials subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle 1.EGSS: 0/1: 29% vs. 14% 2 grade: 33% vs. 19% Inflam: 55% vs. 35% Noninflam: 45% vs. 29% 2.EGSS: 0/1: 28% vs. 11% 2 grade: 37% vs. 14% Inflam: 54% vs. 23% Noninflam: 41% vs. 19%	AR: application site pain, exfoliation, irritation W&P: Colitis, UV light exposure
EPIDUO® FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% NDA 207917 (2015)	Topical treatment of acne vulgaris	Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing	A 12-week R, DB, VC trial subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle IGA: 33.7% vs. 11.0% Inflam:27.8% vs. 13.2% Noninflam:40.5% vs19.7%	AR: skin irritation, eczema, atopic dermatitis, and skin burning sensation. W&P: UV light exposure, local cutaneous reactions

Source: Modified from Table 2, NDA 209353 Clinical Review by Patricia Brown, MD
Abbreviations: GAAS = Global Acne Assessment Score, AR = adverse reaction, W&P = Warnings and Precautions, R = randomized, DB = double-blind, IGSA = Investigator's Global Static Assessment, VC = vehicle controlled, IGA = Investigator's Global Assessment, EGSS = Evaluator's Global Severity Score, Inflam = inflammatory, Noninflam = noninflammatory, UV = ultraviolet

Table 3: Examples of Systemic Acne Products

Generic Name	Brand Name	Formulations	Applicant	Indication
Oral Antibiotics				
Sarecycline	SEYSARA	Tablets; 60, 100, 150 mg	Almirall	Inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older
Minocycline Hydrochloride	SOLODYN	Extended release tablets 55 mg, 65 mg, 105 mg, 115 mg	Medicis	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older
Doxycycline hyclate	DORYX MPC	Delayed release tablets, 60 & 120 mg	Mayne Pharma	In severe acne may be useful adjunctive therapy
	Doxycycline hyclate	Delayed release tablets, 75, 100, 150, 200 mg		
Doxycycline Monohydrate	Monodox	Capsule; 50 mg,75 mg, 100 mg	Aqua Pharms	
Tetracycline Hydrochloride	Tetracycline hydrochloride	Capsule; 250 mg, 500 mg	Heritage Pharms Inc	
Oral Retinoids				
Isotretinoin	ABSORICA	Capsules; 10, 20, 25, 30, 35, 40 mg	Ranabxy	Severe recalcitrant nodular acne in patients 12 years of age and older
	AMNESTEEM Generic	Capsules; 10, 20, 40 mg	Mylan Pharms Inc.	
	CLARAVIS Generic	Capsules; 10, 20, 30, 40 mg	Teva Pharms USA	
	MYORISAN Generic		Douglas Pharm	
	ZENATANE Generic		Dr Reddy's Labs, Ltd	
Hormonal Therapies				
Drospirenone 3 mg/ethinyl estradiol 0.02 mg	Yaz	Tablets	Bayer Healthcare	Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control
Norgestimate 0.180, 0.215, 0.250 mg/ ethinyl estradiol .035 mg	Ortho-cyclen	Tablets	Janssen Pharmaceuticals	Moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche
Norgestimate 0.250 mg/ethinyl estradiol .035 mg	Ortho tri-cyclen			

Source: Adapted from Table 1, NDA 209269 Clinical review by Patricia Brown

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because minocycline foam, 4% 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, 4% under investigational new drug (IND) application 122770 using the 505(b)(2) regulatory pathway. The Applicant selected SOLODYN® Extended Release Tablets (NDA 50808) as 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 Applicant interacted with the Agency during the following meetings: pre-IND (July 30, 2014), End-of-Phase 2 (EOP2, February 17, 2016), a guidance meeting (June 21, 2017), Pre-NDA (February 14, 2018), and a guidance meeting with written responses sent on November 26, 2018. Key points from these meetings are discussed below.

The Agency held a pre-IND meeting with the Applicant on July 30, 2014. The purpose of the meeting was to discuss the development plan for minocycline foam, 4%. In the meeting package, the Applicant proposed to conduct two Phase 3 trials; the Agency provided advice regarding inclusion criteria, the proposed IGA Scale, efficacy endpoints, and safety assessments. The Agency also provided advice regarding the Applicant's proposed pharmacokinetics (PK) trial to be conducted under conditions of maximal use as well as dermal safety studies. The Agency provided information regarding the type of trial design that could serve as the clinical bridge to the Agency's previous findings of systemic nonclinical safety for SOLODYN® Extended Release Tablets.

The Applicant opened the IND with the submission of a protocol for PK/bioavailability trial (FX2014-03; to be conducted in adult subjects) on February 13, 2015. In a "Study May-Proceed" letter dated April 24, 2015, the Agency advised the Applicant of the need to characterize the PK of their product in pediatric subjects aged 9 to <18 years and that their target population should include this age group as well. (b) (4) urthermore, the Agency advised the Applicant that baseline disease severity be defined in the inclusion criteria by IGA scale and lesion count (b) (4) .

For the EOP2 meeting (February 17, 2016), the Applicant asked whether the completed PK/Bioavailability study in adult subjects was sufficient to establish a clinical bridge to the LD. The Agency informed the Applicant that they would also need to conduct a PK study under conditions of maximal use in pediatric subjects age 9 years to 16 years 11 months as well. Such

a trial would need to include an adequate number of subjects at the lowest ages (i.e., 9-10 years of age). The Agency agreed that the Applicant's proposed dermal safety studies may be performed as single-site studies. (b) (4) The Applicant followed the Agency's advice regarding the co-primary endpoint based on IGA but not the endpoint regarding inclusion of inflammatory (b) (4) lesions in lesion counts. The Applicant's co-primary endpoint included inflammatory lesion counts only, and the Applicant stated that they planned to pursue a proposed indication for treatment of inflammatory lesions of acne vulgaris. The Agency also disagreed with certain aspects of the proposed evaluation of safety. For example, the Agency advised the Applicant that evaluation of local tolerability should include assessment for skin hyperpigmentation and that subjects should be queried for unusual headaches and changes in vision.

On April 15, 2016, the Applicant submitted protocols for two Phase 3 trials FX2014-04 and FX2014-05. The protocols were not submitted under a Special Protocol Assessment. The Agency provided advice (letter dated July 17, 2016) regarding the study design, primary and secondary endpoints, and statistical analyses. (b) (4)

Advice regarding study design also included a reminder that subjects who were treatment failures at Week 12 should not continue into the open-label period of the trial.

On November 17, 2016, the Applicant submitted amended Phase 3 protocols. The amended protocols included a revised IGA scale (b) (4) . The Applicant removed the number of lesions from the category descriptors. The Applicant also included additional laboratory assessments, pregnancy testing, and evaluation for skin hyperpigmentation as advised at the EOP2 meeting. On April 4, 2017, the Agency sent an Advice Letter regarding the amended protocols. The Advice Letter mostly reiterated previous comments regarding (b) (4) endpoints and statistical analysis.

The Agency held a guidance meeting with the Applicant on June 21, 2017. In the meeting package, the Applicant revealed that the IGA success rate did not reach statistical significance in Trial FX2014-04. Although the changes in inflammatory and noninflammatory lesion counts were similar between the two trials, the IGA success rate was quite different. The Agency advised the Applicant to re-analyze the data from their Phase 3 trials, including evaluation of results by center to determine the cause of the inconsistent findings between the success on the IGA and lesion counts. The Applicant also asked whether statistically significant findings from a third Phase 3 study would constitute replication of findings from Trial FX2014-05; the

Agency responded yes. The Agency also reiterated that for an acne claim, the study should be designed for both inflammatory and noninflammatory lesions.

The Applicant inquired whether they could use a 5-point ordinal IGA scale in their future Phase 3 trial instead of the 6-point IGA scale used in their previous trials. (b) (4) In response, the Agency noted that the Applicant should consider the labeling implications of using different scales and of using different application instructions. Regarding reuse of study centers, the Agency stated that for independent replication of study findings, new sites are needed for the future clinical trial.

On June 29, 2017, the Applicant submitted a new Phase 3 protocol (FX2017-22). In an Advice Letter dated August 15, 2017, the Agency reiterated comments from the EOP2 meeting regarding the recommended primary endpoints and the proposed statistical analyses. The Applicant followed the Agency's advice regarding the co-primary endpoint based on IGA but not the endpoint regarding lesion counts. The Applicant's co-primary endpoint included inflammatory lesion counts only.

The Agency and the Applicant met for a pre-NDA meeting on February 14, 2018. The Agency provided general guidance regarding the data requirements to support filing, as well as the content and format of the submission. The Agency agreed that the size of the proposed safety database appears reasonable to support the submission of an NDA for minocycline foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. The Agency advised the Applicant regarding information to be included in the 120-day safety update. The Agency also informed the Applicant that the container closure system of their product is considered to be a device. In an Advice Letter dated August 10, 2018, the Agency informed the Applicant of the information required to support the device constituent parts of the combination product.

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, 4%.

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 numbers of enrolled subjects, treatment effect, inconsistencies in IGA scores and inflammatory lesion counts, and prior inspectional history. The clinical inspection summary (review by Cheryl Grandinetti, Pharm.D. dated August 9, 2019) included the following results, summarized in Table 4 below.

Table 4: Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
James F. Pehoushek, M.D. Site #15 Advanced Research Associates 6320A Union Hills Drive, #110 Glendale, AZ 85308	FX2014-05	17	NAI
Glen Sussman Site #26 ICCT Research International, Inc. 233 E. Eri.e., Suite 203 Chicago, IL 60611	FX2014-05	31	Refer to discussion below
William Paull, M.D. Site #368 Columbus Regional Research Institute 800 Talbotton Road Columbus, GA 31904	FX2017-22	31	NAI
Pastor Torres, M.D. Site #401 Integrity Clinical Research Center, Inc. 7590 NW 186th Street, Suite 209 Hialeah, FL 33015	FX2017-22	66	2 data discrepancies (considered unlikely to impact overall safety and efficacy results)
Foamix Pharmaceuticals, Inc 520 U.S. Highway 22, Suite 305 Bridgewater, NJ 08807	FX2014-04, FX2014-05, FX2017-22		A Form FDA-483 (Inspectional Observations) was issued. Refer to the Clinical Inspection Summary for further details.

Source: Reviewer's Table
Abbreviation: NAI = no action indicated

Mr. Glen Sussman was the investigator for Site 26 in Trial FX2014-05. Several inspectional observations were noted. These included concerns regarding the quality of IGA scoring and lesion counts as well as delegation of study-related tasks to individuals who were not qualified by education, training, and experience to perform those tasks. In addition, the inspection revealed late medical assessment of a serious adverse event (SAE) as well as under-reporting of non-serious AEs. Furthermore, Mr. Sussman "had neither previously conducted dermatology trials nor routinely dealt with dermatology patients, as he is not a board-certified dermatologist or even a medical doctor. There is also no indication on his curriculum vitae that he has received any other training as a health care professional. Mr. Sussman performed many tasks in the trial that were not commensurate with his education, training, and experience (e.g., the task of phlebotomy and medical assessment of serious adverse events)."

In light of the inspectional findings, the review team decided to exclude the 31 subjects treated at Site 26 from the evaluations of safety and efficacy. The review team otherwise 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 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 AMZEEQ (minocycline) topical foam, 4% indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

SOLODYN® (minocycline hydrochloride) Extended Release Tablets has been used as the LD for this application.

- The Applicant of this 505(b)(2) new drug application 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.

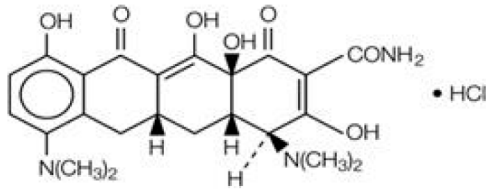
Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval with expiration dating period of 18 months.

Drug Substance

The active ingredient, 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: Minocycline Hydrochloride Molecular Structure



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

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

Drug Product

The drug product, AMZEEQ (minocycline) topical foam, 4% (b) (4) containing micronized minocycline hydrochloride equivalent to 40 mg/g minocycline, filled into aluminum canisters (b) (4) for topical administration. The physician sample canisters are filled with (b) (4) pre-foam formulation (b) (4) ensure delivery of 30 g of foam.

The pre-foam formulation also contains soybean oil, coconut oil, light mineral oil, cyclomethicone (b) (4) cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, and docosanol (b) (4), as inactive ingredients, (b) (4) The propellant (b) (4) consists of (b) (4) butane, isobutane, and propane. The inactive ingredients used in the composition of the drug product are all compendial materials with the exception of docosanol (b) (4) propellant. Sufficient information that supports the use of docosanol and (b) (4) has been provided.

The drug product is manufactured and packaged by the contract manufacturer, ASM Aerosol-Service AG, Switzerland, for Foamix Pharmaceuticals, Inc. in accordance with current good manufacturing practices requirements. It is tested and released according to a specification that includes 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 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 of acne vulgaris is unknown. We requested a consultation from clinical microbiology for advice regarding Section 12.4 (Microbiology) in product labeling. In a review dated July 26, 2019, Dr. Simone Shurland, the clinical microbiology reviewer provided the following comments and recommendations:

"This reviewer is unable to assess the effect of FMX101 (minocycline foam, 4%) treatment of non-nodular moderate to severe acne vulgaris (b) (4) *it is recommended that no microbiology be provided in the labeling. This is consistent with recent NDA applications with similar indications and drug class."*

We concur with the recommendations of the clinical microbiology team and will not include Section 12.4 Microbiology in product labeling.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable. The drug product is packaged in a pressurized aluminum aerosol container (can). The Applicant proposed no other device for drug delivery.

Refer to Section 4.2 Drug Product for information regarding the container/closure system.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for AMZEEQ (minocycline) topical foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older, using SOLODYN® (minocycline hydrochloride) Extended Release Tablets as the listed drug. SOLODYN® has been approved for the same indication in patients 12 years of age and older under NDA 50808 since 2006.

The Applicant has established an adequate clinical bridge to the listed drug, SOLODYN®. Refer to Section 6 Clinical Pharmacology of this review for the details. The Applicant is relying on the Agency's finding of safety for the listed drug. The nonclinical information from the approved label for the listed drug that the Applicant intends to rely on 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 submitted a pivotal 39-week repeat dose minipig dermal toxicity study. Minocycline foams, 4%, 8%, and 16% (corresponding to 10, 20, and 40 mg/kg/day minocycline) were well-tolerated when topically administered (nonoccluded) to Hanford minipigs once daily for 39 weeks. No test article-related adverse effects were noted. No preneoplastic and hyperplastic changes were reported in the skin or any other tissues of the animals. 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 curve (AUC) value associated with this NOAEL (1,160 hr*ng/mL) is 19 times the maximum recommended human dose (MRHD) of AMZEEQ (based on AUC comparison). A dermal carcinogenicity study was not conducted with AMZEEQ based on the results from the 39-week dermal toxicity study with minocycline foam in minipigs.

AMZEEQ does not contain any novel excipients. Several impurities have been identified in the drug substance/product. The Applicant provided impurity profile comparative analysis and scientific rationales with supporting data to support the proposed specifications for these impurities. The Applicant's justifications for these impurities are acceptable from a pharmacology/toxicology perspective.

AMZEEQ is approvable for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older 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 refers to the following DMFs:

DMF [redacted]: minocycline hydrochloride micronized, active, January 16, 2015.

DMF [redacted]: minocycline hydrochloride [redacted] micronized, active, December 6, 2018.

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

5.3. Pharmacology

Primary Pharmacology

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

Minocycline is active against a number of gram-positive and gram-negative organisms, including *Propionibacterium acnes*. The mechanism through which minocycline ameliorates acne is not fully elucidated, although reducing the bacterial count may reduce the size and quantity of lesions by reducing inflammation.

The following information is contained in the SOLODYN® labeling:

The mechanism of action of SOLODYN® for the treatment of acne is unknown.

The pharmacodynamics of SOLODYN® for the treatment of acne are unknown.

Second Pharmacology

None.

Safety Pharmacology

The Applicant did not submit any safety pharmacology studies. Adequate safety pharmacology studies were conducted to support approval of the listed drug (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 toxicokinetics data is provided below. The code name for this drug product is FMX101 Foam.

Type of Study	Major Findings
TK data from general toxicology studies A 3-Week Dermal Toxicity Study of FMX-101 Foam Followed by a 2-Week Recovery Period in Hanford Minipigs (Study # S12919)	Day 1 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 Day 21 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.

Type of Study	Major Findings
A 12-Week Dermal Toxicity Study of FMX-101 Foam with 4-Week Recovery in Hanford Minipigs (Study # S12917)	Day 1 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 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. Day 84 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.

Type of Study	Major Findings
A 39-Week Dermal Toxicity Study of FMX-101 Foam With 4-Week Recovery in Hanford Minipigs (Study # S1314)	Week 4 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): 1,060 ng·hr/mL *Dose proportionality:* Systemic exposure increased roughly dose-proportionally. Week 20 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. Week 39 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): 1,160 ng·hr/mL *Accumulation:* No evidence of systemic accumulation after Week 20.

Type of Study	Major Findings
	Dose proportionality: Systemic exposure increased less than dose-proportionally .

The Applicant conducted a human maximal use pharmacokinetic study in adults to determine biocomparability between AMZEEQ and the listed drug to establish a clinical bridge to the listed drug. It is determined that the Applicant has established an adequate clinical bridge to the listed drug, SOLODYN®. The Applicant also conducted a human maximal use pharmacokinetic study in pediatric subjects (9 years to 16 years 11 months). Refer to the Clinical Pharmacology section of this review for the details.

5.5. Toxicology

5.5.1. General Toxicology

The following nonclinical toxicology studies were reviewed under IND 122770. A summary of these studies is provided below. The code name for this drug product is FMX101 Foam.

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). 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. The NOAEL for both local and systemic toxicity was 11.2% minocycline foam (28 mg/kg/day) based on the results from this study. 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 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). 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 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. The NOAEL for both local and systemic toxicity was 16% minocycline foam (40 mg/kg/day) based on the results from this study. The C_{max} and AUC_{last} values associated with this NOAEL were 82.5 ng/mL and 1,160 hr·ng/mL, respectively. The AUC value associated with this NOAEL (1,160 hr·ng/mL) is 19 times the MRHD of AMZEEQ (based on AUC comparison).

5.5.2. Genetic Toxicology

The following genetic toxicology information is included in the SOLODYN® 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 conducting 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 hyperplastic changes were reported in the skin in the 39-week dermal toxicology study in minipigs.

The following carcinogenicity information is included in the SOLODYN 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:

Teratogenic Effects: Pregnancy Category D

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 postmarketing 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.

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 six animals in a vehicle control group. Animals were topically administered designated dosing formulations in two test phases (induction and challenge). Each animal was dosed three times per week over 3 consecutive weeks during the induction phase followed by one 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 to cause ocular irritation was evaluated using the Organization for Economic Co-operation 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.

Based on an In Vitro Irritancy Score of less than 3, no category can be assigned for the UN GHS categorization of minocycline foam, 4% as defined in OECD Guideline No. 437. According to (b) (4) Protocol (b) (4), minocycline foam, 4% was considered to be a non-irritant to the eye.

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 UN GHS categorization of the test article, as defined in OECD Guideline No. 437. According to (b) (4) Protocol (b) (4), 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 listed drug SOLODYN® in study reports titled "Method Verification and Comparison Study Report for the High Performance Chromatographic Method for Impurities Analysis of Minocycline HCl Foam and Extended Release Tablets"(Study 072638-02-01) and "Screening and Comparison Study Report for Minocycline active pharmaceutical ingredient Impurity Profiles by High Performance Liquid Chromatography" (Study 078873-01-01). The first study (Study 072638-02-01) compared minocycline foam, 4% made with (b) (4) active pharmaceutical ingredient to SOLODYN®. The second study (Study 078873-01-01) compared minocycline foam, 4% made with (b) (4) active pharmaceutical ingredient to SOLODYN®. Table 5 and Table 6 below provide data from these two studies. The code name for this drug product is FMX101 Foam.

Table 5: Impurity Comparison of Minocycline Foam, 4% Manufactured With (b) (4) API to SOLODYN

Sample Formulations	Preparation	% Impurity (b) (4)
Tablet 105 mg SOLODYN	1	
	2	
	3	
	4	
	5	
	6	
	Mean (n=6)	
	%RSD (n=6)	
FMX101 4%	1	
	2	
	3	
	4	
	5	
	6	
	Mean (n=6)	
	%RSD (n=6)	

[1] Below the practical quantitation limit

Abbreviations: API = active pharmaceutical ingredient; RRT = relative retention time; RSD = relative standard deviation; BPQL = below the practical quantitation limit

Table 6: Impurity Comparison of Minocycline Foam, 4% Manufactured With (b) (4) API to SOLODYN

Material	Prep	% Impurity	
		Unknown, RRT	Known
FMX101 4% Lot 6100601	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
FMX101 4% Lot 7080810	1		
	2		
	3		
	4		
	5		
	6		
SOLODYN Tablet Lot 6B6401	1		
	2		
	3		
	4		
	5		
	6		

Abbreviations: API = active pharmaceutical ingredient; RRT = relative retention time; BPQL = below the practical quantitation limit

The impurity profile of minocycline foam, 4% appears similar to that of SOLODYN®. In both tables above, there is only one impurity, (b) (4), in minocycline foam, 4% that is above the International Conference on Harmonization (ICH) Q3B(R2) qualification threshold of 0.2%. However, the levels of (b) (4) are similar to that for the listed drug SOLODYN®. Therefore, no additional nonclinical bridging toxicology studies are considered necessary to address minocycline foam, 4% drug substance or drug product impurities.

The Applicant proposed two specifications for drug product impurities/degradants for minocycline foam, 4%, (b) (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.

Drug Product Excipients

All of the inactive ingredients used in the final marketing formulation are listed in the FDA's Inactive Ingredient Database and are at amounts less than the maximum potency in approved products with exception of soybean oil ((b) (4) in topical product) and coconut oil ((b) (4) in topical product). The proposed excipients are well characterized compendial excipients used in a broad variety of topical and cosmetic

formulations. The amounts of soybean oil and coconut oil, although higher than the maximum potencies listed in the Inactive Ingredient Database, are considered acceptable from a pharmacology/toxicology perspective based on the following:

- Coconut oil is a food-derived product present at a slightly higher level ((b) (4)) than the amount currently listed in the Inactive Ingredient Database.
- Soybean oil is a food-derived product. It is one of the most widely consumed cooking oils.
- Minocyline foam containing (b) (4) soybean oil and (b) (4) coconut oil did not produce any systemic or local adverse effects in minipigs topically administered the drug product over approximately (b) (4) of body surface area for 39 weeks.

6. Clinical Pharmacology

6.1. Executive Summary

In this NDA, the Applicant is seeking approval of minocycline foam, 4% (AMZEEQ) for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older via 505(b)(2) regulatory pathway with SOLODYN® (minocycline hydrochloride) Extended Release Tablet as the listed drug. SOLODYN® was approved for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older on May 8, 2006 (NDA 50808) with oral administration of 1 mg/kg once daily. The Applicant proposed to rely on the Agency's findings of safety for nonclinical toxicology of the listed drug. To support clinical efficacy and safety, the Applicant conducted 10 clinical studies including three randomized double-blinded Phase 3 trials, a dose-finding Phase 2 study, and two maximal use PK studies each in adults and pediatrics.

To establish a bridge between the proposed product and the listed drug, the Applicant conducted a relative bioavailability study (FX2014-03) to compare systemic exposure to minocycline between minocycline foam, 4% administered under maximal use conditions and SOLODYN® in 30 adult subjects. The study results showed that the AUC of minocycline following application of the new 4% foam formulation was approximately 0.1% of AUC following oral administration of SOLODYN®. The study results support the establishment of a clinical bridge of the proposed product with the listed drug SOLODYN®.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed and found this NDA acceptable to support the approval of minocycline foam, 4% from a clinical pharmacology standpoint.

6.1.2. Postmarketing requirement/ postmarketing commitment

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant conducted a relative bioavailability study (FX2014-03) to evaluate systemic exposure to minocycline following topical application with minocycline foam, 4% applied under maximal use conditions (i.e., approximately 4 g dose applied once daily to the face, neck, upper chest, upper back, shoulder, and upper arms) compared to single oral dose of SOLODYN approximately 1 mg/kg in 30 adults with acne vulgaris. Additionally, the Applicant also evaluated PK under maximal use conditions as described above in 20 pediatric patients 10 to less than 17 years of age with acne vulgaris following topical application of minocycline foam, 4% (FX2016-21). It should be noted that there were no 9-year-old subjects in this study; however, there were 6 subjects between 10 and 11 years of age. This reviewer is of the opinion that the available data would support approval down to 9 years of age considering the fact that acne vulgaris is generally less common towards the lower age range.

Of note, the maximum daily dose in the Phase 3 trials was in the range of 2.95 g to 3.52 g per day while dose in the two maximal use studies was approximately 4 g, indicating that maximal use conditions were satisfied in terms of dosing. The PK parameters observed in the two PK studies are summarized in Table 7.

Table 7: PK Parameters of Minocycline in Adult and Pediatric Patients With Acne Vulgaris in Study FX2014-03 and Study FX2016-21

Patient Population	Drug	Dosing Regimen	$AUC_{0\text{-}24h,ss}$ (ng*h/mL) Mean (SD)	$C_{max,ss}$ (ng/mL) Mean (SD)	$T_{max,ss}$ (h) Median (Range)
Adults (N=30)	Solodyn (minocycline ER tablet)	~1 mg/kg, oral single dosing	AUC_{inf} (Day 1): 15474.57 (3690.744)	C_{max} (Day 1): 873.377 (220.046)	T_{max} (Day 1) 3.0 (1.5-4.0)
	Minocycline foam, 4%	~4 g, topical once daily dosing for 21 days	23.02 (10.798)	1.253 (0.645)	14.0 (4.0-23.8)
10 to 11 yrs old (N=6)	Minocycline, foam 4%	~4 g, topical once daily dosing for 7 days	90.9 (90.2)	4.45 (3.97)	12.0 (0-24)
12 to 14 yrs old (N=8)			54.0 (46.2)	2.78 (2.15)	20 (0-24)
15 to <17 yrs old (N=6)			40.8 (23.8)	2.04 (1.17)	6 (0-24)
Pediatrics overall (N=20)			61.1 (59.2)	3.06 (2.68)	12.1 (0-24)

Source: Clinical Study Reports of FX2014-03 and FX2016-21

In adult patients with acne vulgaris, following 21-day topical application of minocycline foam, 4% under maximal use condition, both C_{max} and AUC of minocycline was as low as 0.13% of a single oral dose of Solodyn (~1 mg/kg minocycline). Systemic concentrations appear to be at steady state by day six. This relative bioavailability data supports establishment of a clinical bridge.

Based on cross-study comparison between PK study in adults and adolescent subjects, approximately identical daily dosing of around 4 g produced approximately 2.4-fold and 2.7-fold higher C_{max} and AUC_{0-24h} in adolescent subjects compared to adults. Although the reason for this increased exposure is not known, this could be because of higher dose per body surface area in adolescent subjects compared to adults when administered approximately similar dose of 4 g/day. In spite of observed increase in systemic exposure in adolescent subjects following topical administration, it should be noted that the systemic exposure was low compared to oral administration of SOLODYN®.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a dosing regimen of applying a small amount of topical foam (a cherry-sized amount) to the acne-affected area (such as the face, neck, shoulders, arms, back, or chest), once daily at approximately the same time each day at least 1 hour before bedtime. This proposed regimen is consistent with dosing regimens used in three phase 3 trials (FX2014-04, FX2014-05, and FX2017-22) submitted to support clinical efficacy. Therefore, the efficacy and safety results in phase 3 trials overall support the proposed dosing regimen. For efficacy and safety findings, refer to clinical and statistics reviews in Section 8.

Therapeutic Individualization

Therapeutic individualization based on intrinsic or extrinsic factor is not necessary.

Although in Study FX2016-21, pediatric patients 9 to <17 years of age showed higher exposure than adults following topical application of the proposed product, no dose adjustment is deemed necessary. Pediatric patients 9 to <17 years of age were treated with the same dosing regimen as adult patients in the three phase 3 trials, so efficacy and safety data from pediatric patients in phase 3 trials would support the proposed dosing regimen. For efficacy and safety findings in pediatric patients, refer to clinical and statistics reviews in Section 8.

No studies were conducted for assessment of the effects of extrinsic factors on the pharmacokinetics of the proposed product and this is not deemed necessary as the Applicant has followed a 505(b)(2) regulatory pathway and the systemic exposure of the proposed topical product is lower than the oral listed drug.

Outstanding Issues

There are no outstanding issues that would preclude the approval of minocycline foam, 4% from the clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacological properties and PK characteristics of minocycline foam, 4% are summarized in Table 8.

Table 8: Summary of the Pharmacology and Pharmacokinetics of Minocycline Foam, 4%

Pharmacology	
Mechanism of Action	Per the labeling of Solodyn, the mechanism of action and the pharmacodynamics of minocycline for the treatment of acne is unknown.
Pharmacokinetics	
Adults under maximal use condition (Study FX2014-03)	Adult male and female patients with acne vulgaris (N=30) applied approximately 4 g 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_{0-24h} 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 (~1 mg/kg minocycline), respectively. Steady-state was reached by Day 6 and systemic accumulation of minocycline was not evident.
Pediatrics under maximal use condition (Study FX2016-21)	Pediatric patients 10 to <17 years of age with acne vulgaris applied approximately 4 g of minocycline foam, 4% topically to the face, neck, upper chest, upper back, shoulder and upper arms once daily for 7 days. Minocycline was quantifiable in all subjects obtained on Day 7. The mean ± SD C_{max} and AUC_{0-24h} were 3.1±2.7 ng/mL and 61.1±9.2 ng·h/mL, respectively, which were 2.4-fold and 2.7-fold higher than those observed in adults. At the same dose of approximately 4 g of minocycline foam, 4%, the systemic exposure increased with decrease in age with subjects 10 to 11 years of age and 12 to 14 years of age showing 2.2-fold and 1.3-fold higher AUC values compared to subjects 15 to <17 years of age.
General Information	
Safety/tolerability under maximal use condition	There were no systemic safety concerns observed. In Study FX2014-03, daily application of ~4 g of minocycline foam, 4% for 21 days were safe and well tolerated in adults, and no treatment-emergent-AEs were reported. In Study FX2016-21, daily application of ~4 g of minocycline foam, 4% for 7 days were safe and well tolerated in pediatric 10 to <17 of years of age. Aside from one out of 20 subjects who reported nausea and vomiting, no other treatment-emergent-AEs were reported.
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentrations 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 19.4.2).

Abbreviations: LC-MS/MS = liquid chromatography with tandem mass spectrometry; AE = adverse effects

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of minocycline foam, 4% was not assessed in the maximal use studies, rather it is supported by data from three Phase 3 trials. See Section 8 for details of study design and efficacy results of the Phase 3 trials.

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

Yes. The efficacy and safety data from Phase 3 trials overall supports that the proposed dosing regimen, i.e., applying a small amount to the acne-affected area once daily before bedtime, is acceptable for the treatment of acne vulgaris. See Section 8 for the evaluation of the efficacy and safety of the Phase 3 trials.

Additionally, under maximal use condition, i.e., applying 4 g once daily to the face, neck, shoulders, arms, back, and chest, the systemic exposure was lower than that of the approved listed product, SOLODYN®; therefore, the systemic safety at the maximal use condition of the proposed dosing regimen is adequately supported by the FDA's findings for systemic safety of the approved listed product. See also Section 5 Nonclinical Pharmacology/Toxicology.

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

Alternative dosing regimen for subpopulations for example pediatric population is not needed as the dose and dosing regimen in pediatric subjects down to 9 years of age is supported by safety and efficacy data from the Phase 3 trials as well safety data from the maximal use study in adolescent subjects.

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 performed because the Applicant followed a 505(b)(2) regulatory pathway and the systemic exposure of the proposed topical product was lower than the oral listed drug. Since minocycline is one of tetracycline class drug, theoretical concern for drug interactions for tetracycline class cannot be ruled out unless supported by additional data. Therefore, drug interactions of tetracyclines with anticoagulant and penicillin, which are currently stated on the labeling of the listed product, will be included in the labeling of the proposed product as indicated below:

- Anticoagulants: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

- Penicillin: Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9: Clinical Trials in the NDA 212379 Development Program

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
FX2014-04		Randomized, multicenter, DB, vehicle-controlled, 2-arm safety and efficacy study followed by an OL phase	DB: FMX101 4% QD Vehicle foam QD OL: FMX101 4% QD for up to 40 additional weeks	Co-primary Efficacy: Absolute change from baseline in inflammatory lesion count at Week 12 and 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.	DB Period: 12 weeks OL period: 40 weeks	ITT: DB Period: 466 Age <18 years: 239 Safety population entering OL Period: 284	Subjects ≥9 years of age with acne vulgaris with 20-50 inflammatory lesions, 25-100 noninflammatory lesions, ≤2 nodules on the face, and IGA score 3 (“moderate”) or 4 (“severe”)	US: 35 Dominican Republic: 1

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2014-05		Randomized, multicenter, DB, vehicle-controlled, 2-arm safety and efficacy study followed by an OL phase	DB: FMX101 4% QD Vehicle foam QD OL: FMX101 4% QD for up to 40 additional weeks	Co-primary efficacy: absolute change from baseline in inflammatory lesion count at Week 12 and 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.	DB Period: 12 weeks OL period: 40 weeks	ITT: DB Period: 495 Age <18 years: 233 Safety population entering OL Period: 373	Subjects ≥9 years of age with acne vulgaris with 20-50 inflammatory lesions, 25-100 noninflammatory lesions, ≤2 nodules on the face, and IGA score 3 (“moderate”) or 4 (“severe”)	US: 36 Dominican Republic: 1
FX2017-22		Randomized, multicenter, DB, vehicle-controlled, 2-arm safety and efficacy study	FMX101 4% QD Vehicle foam QD	Co-primary efficacy: absolute change from baseline in inflammatory lesion count at Week 12 and 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	ITT: 1488 Age <18 years: 713	Subjects ≥9 years of age with acne vulgaris with 20-50 inflammatory lesions, 25-100 noninflammatory lesions, ≤2 nodules on the face, and IGA score 3 (“moderate”) or 4 (“severe”)	US: 89

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
FX2010-03		Prospective, multicenter, randomized, DB, vehicle-controlled, parallel group, dose-finding study	FMX101 1% QD FMX101 4% QD Vehicle foam QD	Co-primary Efficacy: The change in the number (co-primary endpoint) of lesion counts (inflammatory, noninflammatory, and total) at Week 12 and 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	ITT: 139 Age <18 years: ?	Subjects 12-25 years of age with acne vulgaris with 20-50 inflammatory lesions, 25-100 noninflammatory lesions, ≤2 nodules, and IGA score 3 (“moderate”) or 4 (“severe”)	Israel: 3
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
FX2014-03		Single-center, nonrandomized, open-label, active-controlled 2-period, 2-treatment crossover bridging PK study under maximal use (MUsT) conditions	Two periods: single oral dose Solodyn® (~1 mg/kg); washout; FMX101 4% ~4 g QD for 21 days	PK of minocycline after multiple doses of FMX101 4% foam; relative bioavailability of FMX101 4% foam compared to Solodyn® (minocycline HCl) extended release tablets	FMX101 4%: 21 days	30	Adults with acne vulgaris and IGA score 3 (“moderate”)	US: 1

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-21		Single-center, nonrandomized, open-label, MUsT/PK bioavailability study in pediatric subjects	FMX101 4% (~4 g) QD to the face, neck, upper chest, shoulders, upper arms, and back	PK of minocycline after multiple doses of FMX101 4% foam under conditions of maximal use	7 days	20	Pediatric subjects age 9 to <17 years; Subjects 12 years to 16 years, 11 months of age, had moderate to severe acne vulgaris on a 5-point IGA scale and acne affecting at least 1 of the following regions: neck, upper chest, upper back, arms; younger subjects may have mild facial acne of more limited extent	US: 1
FX2016-06		Single-center, controlled, randomized, within-subject comparison study to evaluate the phototoxicity potential in healthy adult volunteers – dermal safety study	FMX101 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 FMX101 4%	Single application with follow-up at 21, 45, 69, and 93 hours	32	Healthy adults	US: 1

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-07		Randomized, single-center, controlled, evaluator-blinded, within-subject comparison study to evaluate the sensitizing potential in healthy adult volunteers – dermal safety study	FMX101 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	US: 1
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	FMX101 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	US: 1

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-09		Single-center, controlled, randomized, within-subject comparison study to evaluate the photoallergic skin reaction potential in healthy adult volunteers – dermal safety study	FMX101 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 IP	1 application	56	Healthy adults	US: 1

Source: Clinical Overview, Table 2, pp. 9-10; also Clinical study reports for listed studies
Abbreviations: DB = double-blind; OL = open-label; MUSE = maximum use; PK = pharmacokinetic; QD = once daily; SLS = sodium lauryl sulfate; IGA = Investigator's Global Assessment; IP = investigational product; ITT = intent-to-treat; IP = investigational products; MUSE = maximal use systemic exposure

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of minocycline foam, 4% 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 (SDTM) datasets and Analysis Data Model (ADaM) datasets were submitted. The analysis datasets used in this review are archived at: Application 212379 - Sequence 0001 - 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, 4% for the proposed indication appeared adequate. The finalized Statistical Analysis Plans (SAPs) were submitted to the Agency after the Phase 3 trials were completed and unblinded; this is discussed in more detail in Section 8.1.2 of this review.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

The Applicant conducted three randomized, multicenter, double-blind, vehicle-controlled, Phase 3 trials (FX2014-04, FX2014-05, and FX2017-22) to evaluate the safety and efficacy of AMZEEQ foam, 4%. For all three trials, the key inclusion criteria that defined the study population were identical and are as follows:

- 9 years of age or older
- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- IGA score of 3 ("moderate") or 4 ("severe"), see Table 10 for details on the IGA scale
- No more than 2 nodules on the face

Trials FX2014-04 and FX2014-05 were identically-designed, and the design of Trial FX2017-22 was very similar to that of the other two trials. The only major difference was the planned sample size and randomization ratio. For Trials FX2014-04 and FX2014-05, the protocols specified enrolling and randomizing approximately 450 subjects from approximately 30 investigational sites in a 2:1 ratio to either AMZEEQ foam, 4% (N=300) or vehicle foam (N=150). For Trial FX2017-22, the protocol specified enrolling and randomizing 1500 subjects from approximately 80 investigational sites in a 1:1 ratio to either AMZEEQ foam, 4% (N=750) or

vehicle foam (N=750). In all three trials, subjects applied study product once daily for 12 weeks. Subjects had the following study visits: baseline, and Weeks 1, 3, 6, 9, and 12.

For all three trials, the protocols specified the following co-primary efficacy endpoints:

- Absolute change from baseline in inflammatory lesion counts at Week 12
- Proportion of subjects with IGA treatment success at Week 12, where success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from baseline at Week 12

The protocols for all three trials specified the following as secondary efficacy endpoints:

- Absolute change from baseline in noninflammatory lesion counts at Week 12
- Absolute change from baseline in inflammatory lesion counts and proportion of subjects with IGA treatment success at Week 9
- Absolute change from baseline in inflammatory lesion counts and proportion of subjects with IGA treatment success at Week 6

It should be noted that the finalized statistical analysis plans (SAPs) for the Phase 3 trials have percent change instead of absolute change (b) (4) which are not included in the multiplicity testing strategy, see Section 8.1.2. The previous versions of the SAPs for Trials FX2014-04 and FX2014-05 were submitted for the Agency review and matched the protocols in regard to the secondary endpoints; however, the finalized SAPs were submitted to the Agency after the Phase 3 trials were completed and unblinded. For all three trials, the clinical study reports followed what was specified in the SAPs.

Table 10: Investigator's Global Assessment Scale

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Many noninflammatory lesions. Multiple inflammatory lesions evident with several to many papules/pustules, and there may be one small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may be a few nodulocystic lesions
5	Very severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

Source: pages 33, 33, and 25 of the protocols for Trials FX2014-04, FX2014-05, and FX2017-22, respectively.

8.1.2. Statistical Methodologies

The protocol-specified primary analysis population in all three trials was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocols also specified conducting

supportive analyses using the per-protocol (PP) population. The PP population was defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. The protocols specified that subjects may be excluded from the PP population if any of the following are met:

- Failure to meet inclusion/exclusion criteria
- Have administered any interfering concomitant medications
- Have not, in the opinion of the Investigator, been compliant with the treatment regimen (e.g., reported frequent missed doses)

For the analysis of binary efficacy endpoints, the protocols specified using the Cochran-Mantel-Haenszel test stratified by investigational site. The SAPs specified that if the overall success rate is less than 10%, then the analysis will be done using a two-sample proportion test. For the continuous efficacy endpoints, the protocols specified using analysis of covariance with treatment, baseline value, and investigational site as factors in the model.

The protocol and SAP for both Trials FX2014-04 and FX2014-05 specified using a sequential gatekeeping approach (in the order listed in Section 8.1.1) to control the Type I error rate for testing multiple secondary endpoints. The SAPs specified that both absolute change from baseline in inflammatory lesion counts and proportion of subjects with IGA treatment success at Week 9 need to be statistically significant (i.e., p-value<0.05) in order to test these endpoints at Week 6. For Trial FX2017-22, the protocol and the SAP did not specify a method to control the Type I error rate. In the advice letter sent to the Applicant on August 15, 2017, the Agency stated that the protocol should pre-specify a method to control the Type I error rate for testing multiple secondary efficacy endpoints.

For Trials FX2014-04 and FX2014-05, the protocols specified using the last observation carried forward approach as the primary method to impute missing data; however, the SAPs specified using the MI approach. The clinical study reports for these trials followed the SAPs. For MI, the SAPs specified first imputing intermittent missing data 500 times for each treatment group separately using the Markov Chain Monte Carlo method. For each of the 500 datasets, missing values at scheduled visits (Weeks 3, 6, 9, and 12) are then imputed sequentially using the regression model method for each treatment group separately. For lesion counts, the SAPs specified including lesion counts at previous visits (including baseline) in the model. For IGA scores, the SAPs specified including IGA scores at previous visits (including baseline) in the model. The SAPs also specified using the last observation carried forward, baseline carried forward, and observed case as sensitivity analyses for the handling of missing data for the co-primary efficacy endpoints.

For Trial FX2017-22, the protocols and SAP specified using MI to impute missing data for the co-primary efficacy endpoints. For MI, the SAP specified first imputing intermittent missing data 10 times for each treatment group separately using the Markov Chain Monte Carlo method. For inflammatory lesion count, the SAP specified that the missing data in the 10 datasets for each treatment were to be imputed 10 times using the regression model method, which included inflammatory lesion counts at previous visits (including baseline) in the model. For IGA scores, the SAP specified that the missing data in the 10 datasets for each treatment were to be

imputed 10 times using predictive mean method. The finalized SAP specified that "no variables that have missing values other than inflammatory lesion counts and IGA will be imputed"; therefore, as the Applicant followed the SAP, the Applicant did not impute missing data for the noninflammatory lesion counts in the study report. As previously noted, the finalized SAP for Trial FX2017-22 was submitted to the Agency after the trial was completed and unblinded.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Table 11 presents the disposition of subjects for Trials FX2014-04, FX2014-05, and FX2017-22. The discontinuation rates were generally similar across the three trials. In all three trials, the rate of discontinuation was higher in the vehicle group.

Table 11: Subject Disposition

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
	AMZEEQ (N=307)	Vehicle (N=159)	AMZEEQ (N=312)	Vehicle (N=152)	AMZEEQ (N=738)	Vehicle (N=750)
Discontinued	33 (11%)	31 (19%)	35 (11%)	24 (16%)	89 (12%)	106 (14%)
Adverse Event	0	3 (2%)	1 (<1%)	1 (1%)	3 (<1%)	2 (<1%)
Lost to Follow-up	17 (6%)	9 (6%)	10 (3%)	9 (6%)	34 (5%)	39 (5%)
Subject Request	11 (4%)	10 (6%)	20 (6%)	11 (7%)	36 (5%)	53 (7%)
Protocol Deviation	3 (1%)	2 (1%)	1 (<1%)	1 (1%)	6 (1%)	4 (1%)
Administrative	1 (<1%)	6 (4%)	0	0	0	0
Abnormal Lab Result	0	0	0	0	1 (<1%)	0
Other	1 (<1%)	1 (1%)	3 (1%)	2 (1%)	9 (1%)	8 (1%)

Source: Statistical Reviewer's Analysis; ITT population with Site 26 in Trial FX2014-05 removed.

The demographics for all three trials are presented in Table 12. The demographics were generally balanced across the treatment groups within each trial and were similar in terms of age and sex between the three trials. Trial FX2014-04 had a slightly higher proportion of subjects identify as black or African American compared to the other two trials. In addition, Trial FX2014-05 had a lower proportion of subjects identify as Hispanic or Latino compared to the other two trials.

Table 12: Demographics

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
	AMZEEQ (N=307)	Vehicle (N=159)	AMZEEQ (N=312)	Vehicle (N=152)	AMZEEQ (N=738)	Vehicle (N=750)
Age (years)						
Mean (SD)	20.5 (7.5)	20.0 (8.1)	19.9 (7.0)	20.3 (7.3)	20.2 (7.7)	20.6 (7.8)
Median	18.0	17.0	18.0	17.5	18.0	18.0
Range	11 to 52	10 to 57	10 to 51	11 to 54	9 to 66	9 to 59
Categories						
9-11	2 (<1%)	3 (2%)	5 (2%)	1 (1%)	16 (2%)	15 (2%)
12-17	149 (49%)	85 (53%)	146 (47%)	75 (49%)	349 (47%)	335 (45%)
18+	156 (51%)	71 (45%)	161 (52%)	76 (50%)	373 (51%)	400 (53%)
Sex						
Male	139 (45%)	61 (38%)	132 (42%)	64 (42%)	278 (38%)	281 (37%)
Female	168 (55%)	98 (62%)	180 (58%)	88 (58%)	460 (63%)	469 (63%)
Race						
White	192 (63%)	100 (63%)	237 (76%)	122 (80%)	571 (77%)	560 (75%)
Black/African American	86 (28%)	40 (25%)	58 (19%)	23 (15%)	125 (17%)	144 (19%)
Asian	19 (6%)	10 (6%)	10 (3%)	6 (4%)	25 (3%)	29 (4%)
Multiple	10 (3%)	8 (5%)	6 (2%)	1 (1%)	14 (2%)	10 (1%)
Other	0	1 (1%)	1 (<1%)	0	3 (<1%)	7 (1%)
Ethnicity						
Hispanic or Latino	76 (25%)	36 (23%)	124 (40%)	64 (42%)	266 (36%)	252 (34%)
Not Hispanic or Latino	231 (75%)	123 (77%)	188 (60%)	88 (58%)	472 (64%)	498 (66%)

Source: Statistical Reviewer's Analysis; ITT population with Site 26 in Trial FX2014-05 removed.

Table 13 presents the baseline disease characteristics for all three trials. The baseline disease characteristics were generally balanced across the treatment groups. Trial FX2015-05 had a slightly higher proportion of subjects with an IGA score of 3 ("moderate") at baseline compared to the other two trials.

Table 13: Baseline Disease Characteristics

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
	AMZEEQ (N=307)	Vehicle (N=159)	AMZEEQ (N=312)	Vehicle (N=152)	AMZEEQ (N=738)	Vehicle (N=750)
IGA score						
3 – moderate	255 (83%)	137 (86%)	278 (89%)	140 (92%)	620 (84%)	626 (83%)
4 – severe	52 (17%)	22 (14%)	34 (11%)	12 (8%)	118 (16%)	124 (17%)
Inflammatory lesions						
Mean (SD)	32.2 (8.4)	31.6 (8.6)	31.9 (8.3)	32.3 (7.9)	30.7 (8.9)	30.8 (8.3)
Median	31.0	31.0	30.5	31.0	28.0	29.0
Range	20 to 50	20 to 76	20 to 50	20 to 50	14 to 122	20 to 88
[redacted]						(b) (4)

Source: Statistical Reviewer's Analysis; ITT population with Site 26 in Trial FX2014-05 removed.
Abbreviations: IGA = Investigator's Global Assessment; SD = standard deviation

8.1.4. Results of the Co-Primary Efficacy Endpoints

Table 14 presents the results of the co-primary efficacy endpoints for all three trials in the ITT population. For Trials FX2014-05 and FX2017-22, AMZEEQ was statistically superior to vehicle for both co-primary efficacy endpoints (p-values ≤0.039). For Trial FX2014-04, AMZEEQ was statistically superior to vehicle for absolute change in inflammatory lesion counts at Week 12 (p-value=0.008); however, it was not statistically superior to vehicle for IGA success at Week 12 (p-value=0.181). The results for the PP population (not shown) were similar to those in the ITT population (Table 14). The results of percent change from baseline in inflammatory lesion counts at Week 12 (i.e., an exploratory efficacy endpoint) for all three trials are supportive of the results for the absolute change, see Table 43 in Section 19.5.

As can be seen in Table 14, the results for IGA success in Trial FX2017-22 were much higher compared to the other trials. An additional sensitivity analysis investigating the effect of centers with extreme results can be found in Section 8.1.6.

The results presented in Table 14 for Trial FX2014-05 do not include Site 26; see Section 4.1 for details as to why this site was removed from the safety and efficacy analyses. However, the results with this site included were similar to those in Table 14, see Table 44 in Section 19.5.

Table 14: Results of the Co-Primary Efficacy Endpoints at Week 12 [ITT[1]]

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
Endpoints	**AMZEEQ (N=307)**	**Vehicle (N=159)**	**AMZEEQ (N=312)**	**Vehicle (N=152)**	**AMZEEQ (N=738)**	**Vehicle (N=750)**
IGA success[2]	8.1%	4.8%	15.8%	8.4%	30.8%	19.6%
Difference (95% CI)	3.3% (-1.5%, 8.2%)		7.4% (0%, 13.7%)		11.2% (6.6%, 15.8%)	
P-value[3]	0.181		0.039		<0.001	
Absolute change from baseline in inflammatory lesion counts						
Mean	-14.1	-11.2	-13.2	-10.2	-16.9	-13.4
LS mean[4]	-14.0	-11.2	-13.7	-10.5	-16.4	-12.7
Difference (95% CI)	-2.8 (-4.9, -0.7)		-3.2 (-5.6, -0.9)		-3.7 (-4.8, -2.5)	
P-value[4]	0.008		0.005		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis except for Trial FX2014-05, which excluded Site 26 in the above table)
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an Investigator's Global Assessment (IGA) score of 0 or 1 with at least a 2-grade reduction from baseline.
[3] For Trial FX2014-04, the p-value is based on two-sample proportion test as the overall rate is less than 10%. For Trials FX2014-05 and FX2017-22, the p-value based on a Cochran-Mantel-Haenszel (CMH) test stratified by pooled investigational site.
[4] Least square (LS) mean and p-value are based on analysis of covariance (ANCOVA) with treatment and investigational site as factors, and baseline value as a covariate.

Table 15 presents the number of subjects with missing data for the co-primary endpoints along with the results of the co-primary endpoints across the various prespecified imputation methods. The results were generally similar across the various methods. In all three trials, the results for BOCF were slightly less than the other methods; however, the treatment effect (i.e., difference between AMZEEQ and vehicle) was similar to the other methods.

Table 15: Results for the Co-Primary Efficacy Endpoints at Week 12 With Different Approaches for Handling Missing Data

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
	AMZEEQ (N=307)	Vehicle (N=159)	AMZEEQ (N=312)	Vehicle (N=152)	AMZEEQ (N=738)	Vehicle (N=750)
Subjects with Missing Data	40 (13%)	31 (19%)	38 (12%)	25 (16%)	112 (15%)	128 (17%)
IGA Success[1]						
MI (primary)	8.1%	4.8%	15.8%	8.4%	30.8%	19.6%
Observed	8.6%	4.7%	16.1%	8.3%	31.8%	21.4%
LOCF	7.7%	4.0%	14.7%	7.5%	29.3%	19.2%
BOCF	7.5%	3.8%	14.1%	7.2%	27.0%	17.7%
Absolute Change in Inflammatory Lesion Counts						
MI (primary)	-14.0	-11.2	-13.5	-10.3	-16.4	-12.7
Observed	-14.0	-11.3	-14.0	-10.7	-16.8	-12.9
LOCF	-13.8	-10.5	-13.7	-10.3	-16.1	-12.3
BOCF	-12.3	-9.4	-12.3	-8.9	-14.4	-10.7

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis except for Trial FX2014-05, which excluded Site 26 in the above table)
[1] Success is defined as an IGA score of 0 or 1 with at least a 2-grade reduction from baseline.
Abbreviations: IGA = Investigator's Global Assessment Scale; MI = multiple imputation; LOCF = last observation carried forward; BOCF = baseline observation carried forward

8.1.5. Results of the Secondary Efficacy Endpoints

As noted in Section 8.1.2, the Applicant did not control the Type I error for testing multiple secondary efficacy in Trial FX2017-22 as neither the protocol nor the finalized SAP specified an approach. Therefore, the results of the secondary efficacy endpoints for Trial FX2017-22 are viewed as exploratory for this review. In addition, the co-primary efficacy endpoint of IGA success at Week 12 was not statistically significant for Trial FX2014-04; therefore, the secondary efficacy endpoints for this trial cannot be tested for statistical significance as the protocol and SAP for this trial specified a sequential gatekeeping approach to control the Type I error.

(b) (4)

Table 17 presents the results for the secondary efficacy endpoints of IGA success and absolute change in inflammatory lesion counts at Weeks 6 and 9. For Trial FX2017-05, AMZEEQ was not statistically superior to vehicle for IGA success at Week 9; therefore, the IGA success and absolute change in inflammatory lesions at Week 6 cannot be tested per the multiplicity testing strategy.

Table 17: Results for the Secondary Efficacy Endpoints of IGA Success and Absolute Change in Inflammatory Lesion Counts at Weeks 6 and 9 [ITT[1]]

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
Endpoints	**AMZEEQ (N=307)**	**Vehicle (N=159)**	**AMZEEQ (N=312)**	**Vehicle (N=152)**	**AMZEEQ (N=738)**	**Vehicle (N=750)**
Week 9						
IGA success[2]	4.2%	1.4%	7.8%	6.4%	20.5%	11.7%
Difference (95% CI)	2.8% (-0.3%, 5.8%)		1.4% (-3.9%, 6.6%)		8.8% (5.0%, 12.7%)	
P-Value[3]	*		0.553		*	
Absolute change in Inflammatory lesion Counts						
Mean	-13.8	-9.3	-12.8	-9.1	-16.1	-12.3
LS mean[4]	-13.2	-8.8	-13.3	-9.4	-15.6	-11.7
Difference (95% CI)	-4.4 (-6.4, -2.4)		-3.8 (-6.2, -1.5)		-3.9 (-5.0, -2.8)	
P-value[3]	*		0.002		*	
Week 6						
IGA success[2]	3.5%	0.8%	5.0%	0.9%	11.6%	6.5%
Difference (95% CI)	2.7% (0.1%, 5.3%)		4.1% (1.1%, 7.1%)		5.1% (2.1%, 8.0%)	
P-value[3]	*		*		*	
Absolute change in Inflammatory lesion Counts						
Mean	-12.0	-8.1	-11.8	-8.1	-13.6	-10.2
LS mean[4]	-11.6	-7.8	-12.8	-9.0	-13.1	-9.6
Difference (95% CI)	-3.9 (-5.9, -1.8)		-3.9 (-6.0, -1.7)		-3.5 (-4.6, -2.4)	
P-value[4]	*		*		*	

Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an IGA score of 0 or 1 with at least a 2-grade reduction from baseline.
[3] For Trials FX2014-04 and FX2014-05, the p-value is based on two-sample proportion test as the overall rate is less than 10%. For Trials FX2017-22, the p-value based on a Cochran-Mantel-Haenszel (CMH) test stratified by pooled investigational site.
[4] Least square (LS) mean and p-value are based on analysis of covariance (ANCOVA) with treatment and pooled investigational site as factors, and baseline value as a covariate.
* For Trial FX2014-04, the secondary efficacy endpoints cannot be tested as the co-primary efficacy endpoint of Investigator's Global Assessment (IGA) success at Week 12 was not statistically significant. For Trial FX2014-05, IGA success at Week 9 was not statistically significant; therefore, the endpoints at Week 6 cannot be tested. For Trial FX2017-22, the protocol and SAP did not specify a method to control the Type I error rate.

8.1.6. Additional Sensitivity Analysis

As noted in Section 8.1.4, the response rates for IGA success in Trial FX2017-22 in both treatment groups were much higher in comparison to the other two trials. A sensitivity analysis was conducted where centers with extreme results for IGA success were removed from the analysis to investigate their impact on the overall results. The sensitivity analysis was limited to extreme centers that had a sample size of at least 12. Table 18 presents the 9 extreme centers identified. The table also presents the results for co-primary efficacy endpoints at Week 12 for both the combined extreme centers and with the extreme centers removed. A total of 263 subjects (130 AMZEEQ and 133 vehicle) are included in the extreme centers, which amounts to approximately 18% of the total sample size in the trial. By removing the extreme centers, the

IGA success rate decreased from 30.8% to 24.0% for the AMZEEQ group and decreased from 19.6% to 14.1% for the vehicle group. The results for absolute change in inflammatory lesions also decreased in both treatment groups; however, the treatment effect (i.e., difference between the two groups) remained the same.

Table 18: Sensitivity Analysis for the Co-Primary Efficacy Endpoints at Week 12 Based on Extreme Analysis Centers in Trial FX2017-22 [ITT[1]]

	IGA Success[2]		Absolute Change in Inflammatory Lesions	
	AMZEEQ (N=738)	Vehicle (N=750)	AMZEEQ (N=738)	Vehicle (N=750)
Extreme Centers				
401 (N_A=33, N_V=33)	72.7%	66.7%	-19.6	-20.0
346 (N_A=24, N_V=26)	63.9%	57.7%	-27.9	-28.2
368 (N_A=15, N_V=16)	62.1%	29.4%	-26.0	-18.7
403 (N_A=13, N_V=14)	58.2%	43.2%	-25.9	-16.3
347 (N_A=13, N_V=12)	56.5%	70.8%	-25.6	-29.3
340 (N_A=11, N_V=12)	55.5%	31.3%	-22.9	-17.0
389 (N_A=9, N_V=8)	46.8%	1.0%	-20.7	-4.7
303 (N_A=6, N_V=6)	46.3%	5.5%	-18.5	-20.5
308 (N_A=6, N_V=6)	76.0%	0%	-16.3	-11.6
Results for Extreme Centers	N=130	N=133	N=130	N=133
Response[3,4]	62.5%	45.4%	-21.6	-18.4
Difference	17.0%		-3.2	
Results Excluding Extreme Centers	N=608	N=617	N=621	N=617
Response[3,4]	24.0%	14.1%	-15.0	-11.2
Difference	10.0%		-3.7	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an Investigator's Global Assessment (IGA) score of 0 or 1 with at least a 2-grade reduction from baseline.
[3] For IGA success, response is the average over the imputed data sets.
[4] For inflammatory lesions, response is the LS mean. The LS means are based on analysis of covariance (ANCOVA) with treatment and pooled investigational site as factors, and baseline value as a covariate.

8.1.7. Findings in Special/Subgroup Populations

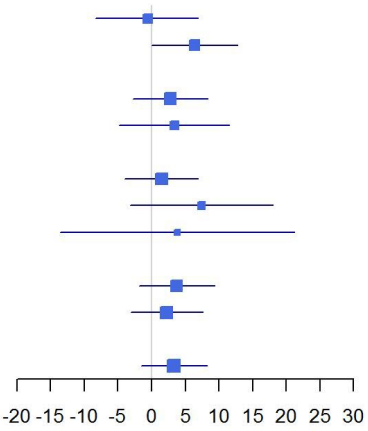
8.1.7.1. Sex, Age, Race, and Baseline IGA Score

The results for IGA success at Week 12 by sex, age (9-17 and 18+ years), race (White, Black, and Other), and baseline IGA scores for Trials FX2014-04, FX2014-05, and FX2017-22 are presented in Figure 2, Figure 3, and Figure 4, respectively. The results for absolute change in inflammatory lesion counts at Week 12 by these same subgroups for Trials FX2014-04, FX2014-05, and FX2017-22 are presented in Figure 5, Figure 6, and Figure 7, respectively.

In Trial FX2014-05, black subjects in the vehicle group had a larger decrease in inflammatory lesion counts than black subjects in the AMZEEQ group; however, this effect was not observed for IGA success, nor observed in the other two trials. The observation of reversed treatment effect in the subgroup of black subjects in Trial FX2014-05 may be attributed to the small sample size in this subgroup treated with vehicle (i.e., 23 subjects).

Figure 2: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2014-04 [ITT[1]]

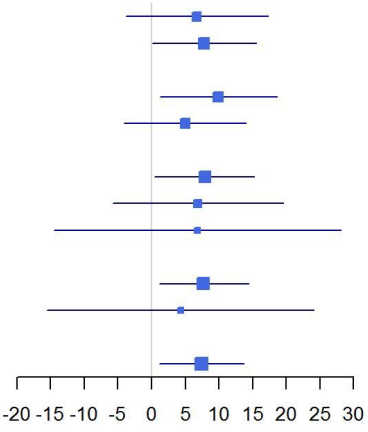
Subgroups (n[A], n[V])	AMZEEQ (N=307)	Vehicle (N=159)	Difference
Sex			
Males (139, 61)	5.4%	6.1%	-0.6%
Females (168, 98)	10.3%	3.9%	6.4%
Age			
9-17 (151, 88)	5.8%	3.0%	2.8%
18+ (156, 71)	10.3%	6.9%	3.4%
Race			
White (192, 100)	5.4%	3.9%	1.5%
Black (86, 40)	13.2%	5.8%	7.4%
Other (29, 19)	10.9%	7.1%	3.8%
Baseline IGA			
3 - Moderate (255, 137)	9.2%	5.5%	3.7%
4 - Severe (52, 22)	2.4%	0.2%	2.2%
Overall	8.1%	4.8%	3.3%



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviations: IGA = Investigator's Global Assessment; CI = confidence interval

Figure 3: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2014-05 [ITT[1]]

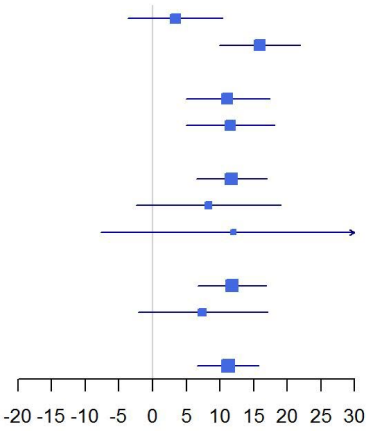
Subgroups (n[A], n[V])	AMZEEQ (N=312)	Vehicle (N=152)	Difference
Sex			
Males (132, 64)	17.6%	10.9%	6.7%
Females (180, 88)	14.4%	6.6%	7.8%
Age			
9-17 (151, 76)	17.4%	7.5%	9.9%
18+ (161, 76)	14.3%	9.3%	5.0%
Race			
White (237, 122)	17.3%	9.4%	7.9%
Black (58, 23)	11.6%	4.7%	6.9%
Other (17, 7)	9.2%	2.3%	6.8%
Baseline IGA			
3 - Moderate (278, 140)	16.1%	8.4%	7.7%
4 - Severe (34, 12)	12.9%	8.6%	4.3%
Overall	15.8%	8.4%	7.4%



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviation: IGA = Investigator's Global Assessment

Figure 4: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2017-22 [ITT[1]]

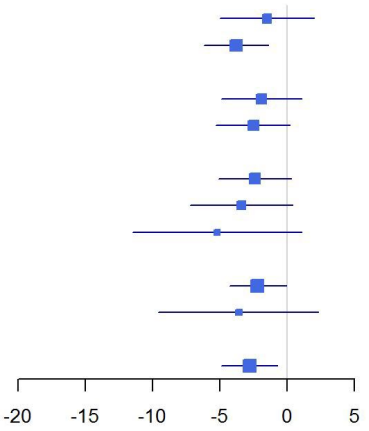
Subgroups (n[A], n[V])	AMZEEQ (N=738)	Vehicle (N=750)	Difference
Sex			
Males (278, 281)	22.9%	19.5%	3.4%
Females (460, 469)	35.6%	19.7%	15.9%
Age			
9-17 (365, 350)	27.7%	16.6%	11.1%
18+ (373, 400)	33.8%	22.3%	11.5%
Race			
White (571, 560)	31.2%	19.5%	11.7%
Black (125, 144)	27.3%	19.0%	8.3%
Other (42, 46)	35.3%	23.2%	12.0%
Baseline IGA			
3 - Moderate (620, 626)	32.8%	21.0%	11.8%
4 - Severe (118, 124)	20.0%	12.6%	7.4%
Overall	30.8%	19.6%	11.2%



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviation: IGA = Investigator's Global Assessment

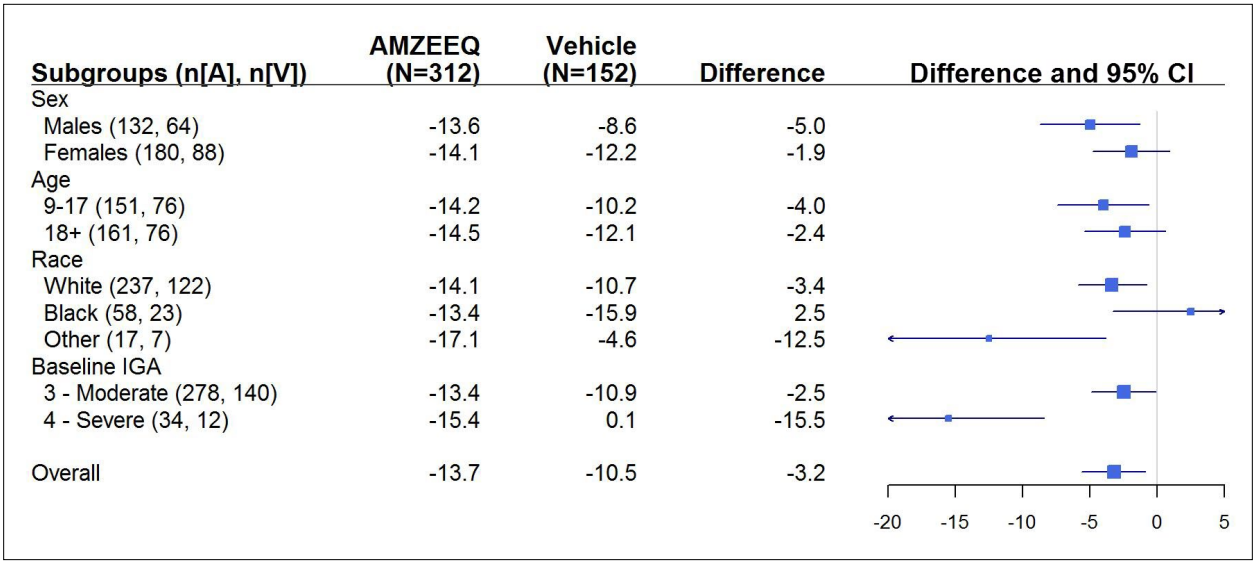
Figure 5: Absolute Change in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2014-04 [ITT[1]]

Subgroups (n[A], n[V])	AMZEEQ (N=307)	Vehicle (N=159)	Difference
Sex			
Males (139, 61)	-12.0	-10.5	-1.5
Females (168, 98)	-15.3	-11.5	-3.8
Age			
9-17 (151, 88)	-12.8	-10.9	-1.9
18+ (156, 71)	-15.3	-12.8	-2.5
Race			
White (192, 100)	-14.1	-11.7	-2.4
Black (86, 40)	-14.7	-11.3	-3.4
Other (29, 19)	-17.2	-12.0	-5.2
Baseline IGA			
3 - Moderate (255, 137)	-14.0	-11.8	-2.2
4 - Severe (52, 22)	-11.2	-7.6	-3.6
Overall	-14.0	-11.2	-2.8



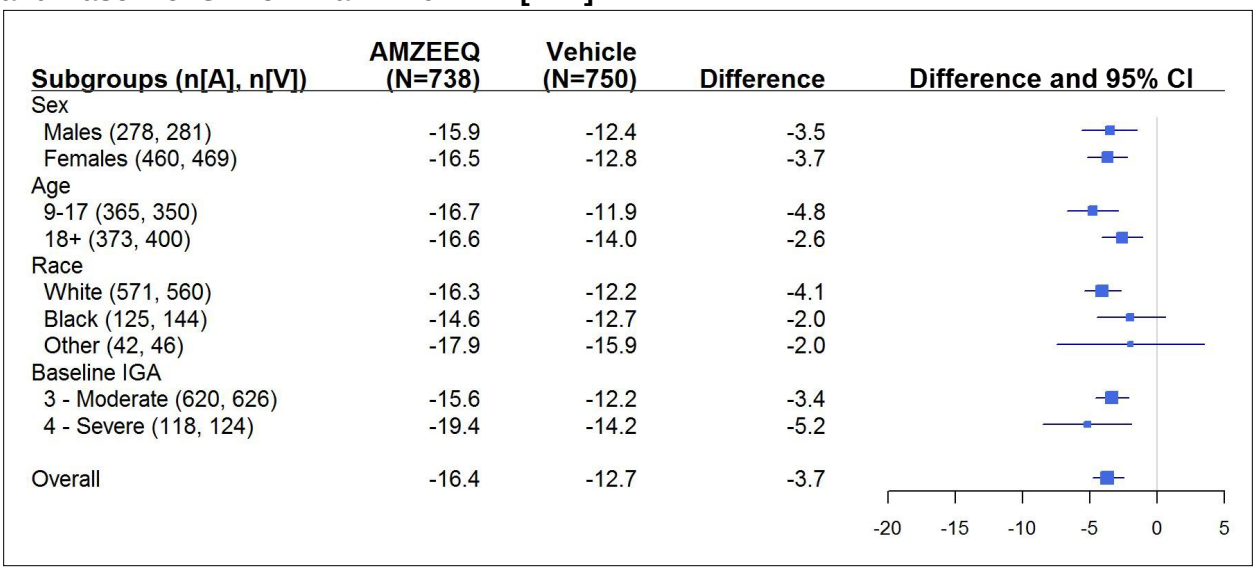
Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviation: IGA = Investigator's Global Assessment

Figure 6: Absolute Change in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2014-05 [ITT[1]]



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviation: IGA = Investigator's Global Assessment

Figure 7: Absolute Change in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA for Trial FX2017-22 [ITT[1]]



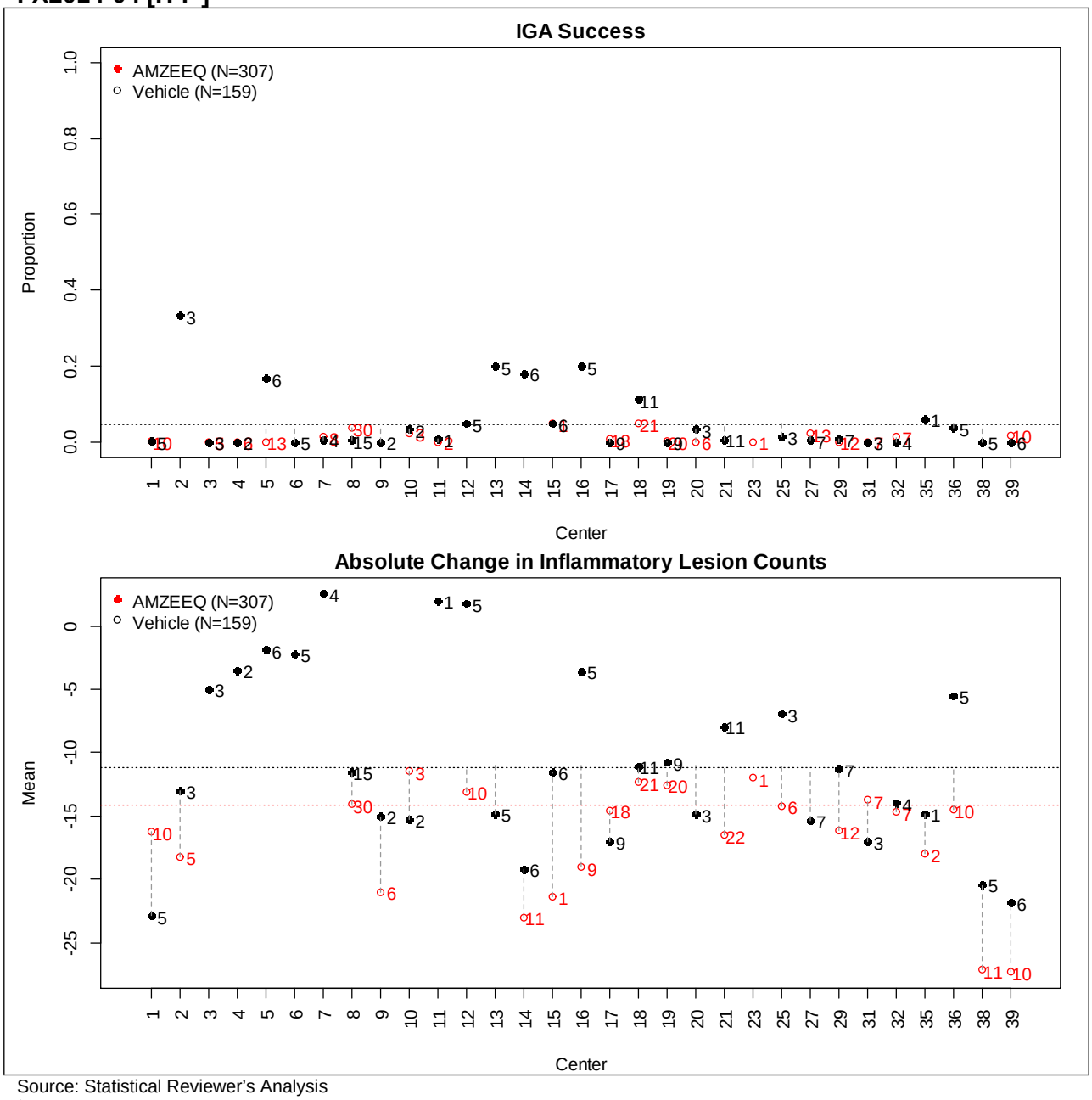
Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Abbreviation: IGA = Investigator's Global Assessment

8.1.7.2. Center

Trial FX2014-04 enrolled and randomized 466 subjects from 31 centers. Trial FX2014-05 enrolled and randomized 464 subjects from 36 centers (excluding Site 26 which had 31 subjects). Trial FX2017-22 enrolled and randomized 1488 subjects from 89 centers. Figure 8, Figure 9, and Figure 10 present the results for the co-primary efficacy endpoints at Week 12 by

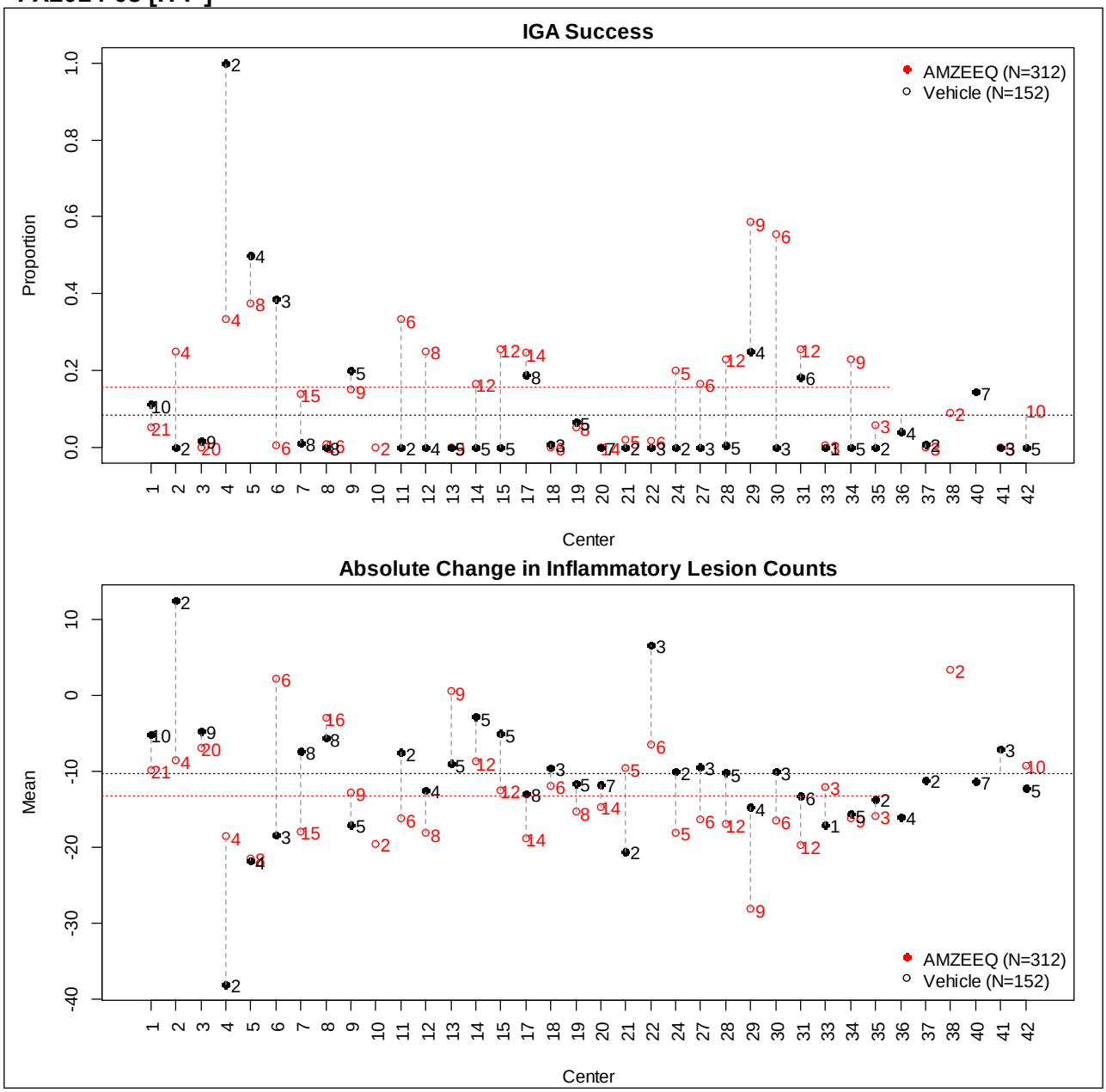
analysis center. As noted in Section 8.1.6, Trial FX2017-22 had several centers with high response rates for IGA success at Week 12.

Figure 8: Results for the Co-Primary Efficacy Endpoints at Week 12 by Center for Trial FX2014-04 [ITT[1]]



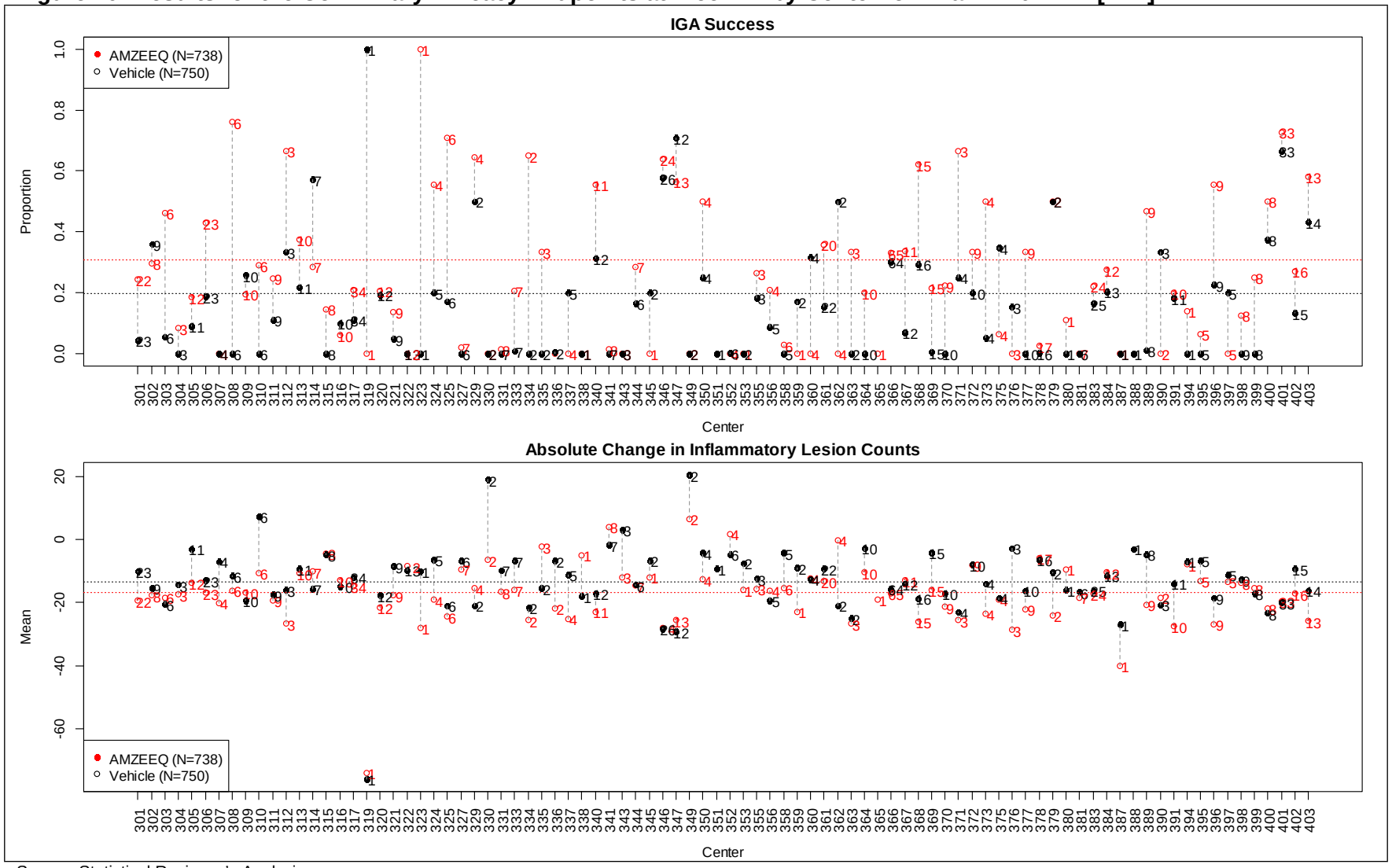
Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI). The values displayed are the averages over the imputed datasets.
[2] The dotted horizontal line denotes the overall result for each treatment group (red for AMZEEQ and black for vehicle).

Figure 9: Results for the Co-Primary Efficacy Endpoints at Week 12 by Center for Trial FX2014-05 [ITT[1]]



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI). The values displayed are the averages over the imputed datasets.
[2] The dotted horizontal line denotes the overall result for each treatment group (red for AMZEEQ and black for vehicle).

Figure 10: Results for the Co-Primary Efficacy Endpoints at Week 12 by Center for Trial FX2017-22 [ITT[1]]



Source: Statistical Reviewer's Analysis
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI). The values displayed are the averages over the imputed datasets.
[2] The dotted horizontal line denotes the overall result for each treatment group (red for AMZEEQ and black for vehicle).

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for minocycline foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris focuses on pooled data from three Phase 3 trials, FX2014-04, FX2014-05, and FX 2017-22. Trials FX2014-04 and FX2014-05 were randomized, multicenter, double-blind, vehicle-controlled, 2-arm safety and efficacy studies followed by an open-label phase. These trials were of identical design with the double-blind treatment period lasting 12 weeks and the open-label period lasting 40 weeks. Trial FX2017-22 was a randomized, double-blind, multicenter, vehicle-controlled, 2-arm safety and efficacy study which had a 12-week double-blind treatment period but no open-label treatment period.

The Phase 3 study population included a total of 2418 subjects ages 9 years and older with moderate to severe acne vulgaris defined as 20-50 inflammatory lesions, 25-100 noninflammatory lesions, ≤2 nodules on the face, and IGA score 3 or 4. Subjects were randomized 2:1 in Trial FX2014-04 and FX 2014-05 and 1:1 in FX2017-22 to treatment with minocycline foam, 4% or vehicle foam. Subjects applied study drug to acne-affected areas (face, neck, back, etc.) once daily, up to a total of 4 grams per dose. Investigators conducted safety and efficacy assessments at Weeks 1, 3, 6, 9, and 12 during the double-blind period for all three trials and every 6 weeks from Week 16 to 52 for Trial FX2014-04 and FX 2014-05.

The safety population as defined and discussed in the next section of this review included 1356 pediatric (age 9 years and older) and adult subjects treated with minocycline foam, 4%. As discussed in Section 4.1 of this review, subjects from Site 2014-05-26 were excluded from the safety population.

The Applicant also submitted supportive safety data from a Phase 2 dose-finding trial, two PK/Bioavailability studies conducted under conditions of maximal use (one in adult subjects and one in pediatric subjects age 9 to <17 years), and 4 dermal safety studies.

To determine the safety profile of minocycline foam, 4% , 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.

The Applicant also submitted a 120-day safety update (SDN 18; June 20, 2019). The update contained new information regarding 2 pregnancies which occurred during the development program. Pregnancy outcomes will be discussed in more detail in Section 8.2.4 of this review.

At the End of Phase 2 meeting, the Agency informed the Applicant that the potential for QT/QTc prolongation from their product should be addressed. In the Summary of Clinical Safety, the Applicant provided a risk assessment of the proarrhythmic potential of minocycline foam, 4%. This is discussed in more detail in Section 8.2.4 of this review.

8.2.2. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of safety for minocycline foam, 4% included pooled data from Phase 3 Trials FX2014-04, FX2014-05, and FX2017-22 (i.e., the Phase 3 Primary Pool). Subjects from Site 2014-05-26 were excluded; refer to Section 4.1 of this review for more details. Data from the Phase 1 and 2 studies were not integrated because of dissimilar study designs and different dose regimens.

The safety population includes all randomized subjects who received at least one dose of the study medication during double-blind treatment in the three Phase 3 studies and has been analyzed according to the treatment that subjects received. For Studies FX2014-04 and FX2014-05, the ITT and Safety Populations were identical (N=466 and N=464 [495 before removal of Site 26], respectively). For Study FX2017-22, a total of four subjects were discovered to be randomization errors upon database query (2 were screen failures and 2 were lost to follow-up with no further contact after the baseline visit), and thus the Safety Population was comprised of 1484 subjects (ITT population, N=1488).

In the 3 Phase 3 trials, a total of 1048 subjects applied minocycline foam, 4% for 12 weeks or longer. Of these subjects, a total of 530 were exposed for 6 months or longer, and 227 subjects for 1 year or longer. Duration of exposure by age group is displayed in Table 19 below.

Table 19: Exposure Summary by Age Group, Phase 3 Primary Pool*

Duration of Exposure	FMX101 4% n=1356			Vehicle Foam n=1058			Totals n=2414
	9 – 12 years	13 – 17 years	≥18 years	9 - 12 years	13 - 17 years	≥18 years	
≥12 weeks	53 (3.9%)	490 (36.1%)	505 (37.2%)	9 (0.9%)	90 (8.5%)	75 (7.1%)	1222 (50.6%)
≥6 months	15 (1.1%)	191 (14.1%)	175 (12.9%)	7 (0.7%)	80 (7.6%)	62 (5.9%)	530 (22.0%)
≥1 year	11 (0.8%)	119 (8.8%)	97 (7.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	227 (9.4%)

Source: Reviewer's Table created in JReview using ISS dataset
* Excluding Site 26 and using timepoints defined by the Applicant (>6 months = >168 days, >1 year= >350 days)

The Applicant summarized exposure using treatment duration in days during the double-blind and open-label periods of the Phase 3 trials. Only Trials FX2014-04 and FX2014-05 included an open-label period. The mean treatment duration during the double-blind period of the Phase 3 trials was 80.7 days in the minocycline foam, 4% group and 78.8 days in the vehicle group. The duration of the double-blind period was 12 weeks (84 days).

During the open-label period, treatment could be suspended if acne improved or resolved, and resumed if acne recurred or worsened. The overall mean duration of treatment with minocycline foam, 4% during the 40-week open-label period was 235.2 days.

Relevant characteristics of the safety population

The demographics of the safety population are similar to the ITT population. In the Phase 3 Primary Pool, the majority of the subjects were White (73.7%), female (60.4%), not Hispanic/Latino (66.2%), and 18 years of age and older (51.1%). The demographic

characteristics of both treatment groups were comparable. One subject was 65 years of age or older. Most subjects resided in the United States, although 2 of the Phase 3 trials included one site in the Dominican Republic. Refer to Appendix 19.5 for demographic characteristics of subjects in the safety population.

Adequacy of the Safety Database

The total subject exposure to minocycline foam, 4% 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, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris.

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, 4%. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For the Phase 3 trials, 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 treatment-emergent AE (TEAE) was defined as "an AE that emerged during treatment having been absent pretreatment or worsened relative to the pretreatment 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
- 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.

A Serious AE (SAE) was defined as an AE that was:

- 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, and local skin tolerability assessment scores greater than zero, 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 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

During the Phase 3 trials, investigators conducted safety assessments during clinic visits at Weeks 1, 3, 6, 9, and 12. During the open-label period of Trials FX2014-04 and FX2014-05, subjects returned for visits at Week 16, then every 6 weeks until Week 52. The evaluation of safety included vital signs (blood pressure and heart rate), local skin tolerability assessments (erythema, dryness, hyperpigmentation, and skin peeling at the sites of study drug application), and general physical examinations. As part of the physical examinations during the double-blind periods in Phase 3 Studies FX2014-04 and FX2014-05, 12-lead electrocardiograms (ECGs) were performed only in subjects older than 39 years.

The Phase 3 protocols included clinical laboratory testing at screening, Week 3, and Week 12 during the double-blind period, and at Week 28 and during the final visit of the open-label period in Trials FX2014-04 and FX2014-05. Laboratory assessments included hematology, serum chemistry, and urinalysis. In addition, urine pregnancy tests (UPTs) were performed on all females of childbearing potential at baseline, Weeks 3, 6, 9, and 12 and final visit or when a subject prematurely withdrew from the study. For the open-label periods, home pregnancy kits were provided at each visit to all female subjects of childbearing potential, which were to be used at least monthly and if a pregnancy was suspected between visits (e.g., if a subject missed her period). A UPT was also performed at Week 52/ final visit.

Investigators assessed local skin tolerability (erythema, dryness, hyperpigmentation, and skin peeling at the sites of study drug application) at each visit on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Itching was assessed using the same scale based on the subjects' subjective assessment.

8.2.4. Safety Results

Deaths

There were no deaths in the development program for minocycline foam, 4%.

Serious Adverse Events

In the Phase 3 Primary Pool (Trials FX2014-04, FX2014-05, and FX2017-22) during the double-blind period, 11 subjects experienced 14 serious adverse events (SAEs): 6 (0.4%) subjects treated with minocycline foam, 4% experienced seven SAEs and 5 (0.5%) subjects treated with vehicle foam experienced seven SAEs. These SAEs are displayed in Table 20 below.

Table 20: Treatment -Emergent SAEs, Phase 3 Primary Pool During Double-Blind Period

	Minocycline Foam, 4% n=1356	Vehicle Foam n=1058
Pregnancy, puerperium and perinatal conditions	2 (0.1%)	1 (0.1%)
Abortion spontaneous	1 (0.1%)	1 (0.1%)
Ectopic pregnancy	1 (0.1%)	0 (0.0%)
Injury, poisoning and procedural complications	1 (0.1%)	0 (0.0%)
Facial bones fracture	1 (0.1%)	0 (0.0%)
Gastrointestinal disorders	1 (0.1%)	3 (0.3%)
Intestinal perforation	1 (0.1%)	0 (0.0%)
Intestinal obstruction	1 (0.1%)	1 (0.1%)
Enteritis	0 (0.0%)	1 (0.1%)
Gastritis	0 (0.0%)	1 (0.1%)
Esophageal stenosis	0 (0.0%)	1 (0.1%)
Psychiatric disorders	1 (0.1%)	0 (0.0%)
Suicide attempt	1 (0.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.1%)	0 (0.0%)
Asthma	1 (0.1%)	0 (0.0%)
Hepatobiliary disorders	0 (0.0%)	2 (0.2%)
Cholecystitis	0 (0.0%)	1 (0.1%)
Biliary dyskinesia	0 (0.0%)	1 (0.1%)
Events	7	7
Subjects	6 (0.4%)	5 (0.5%)

Source: Reviewer's Table created in JReview using ISS dataset
Abbreviation: SAEs = serious adverse events

Four events in three subjects treated with minocycline foam, 4% and five events in three subjects treated with vehicle were classified as severe intensity. Two SAE (ectopic pregnancy and spontaneous abortion) in two subjects treated with minocycline foam,4% and one SAE (spontaneous abortion) in a subject treated with vehicle resulted in discontinuation of treatment.

During the open-label period, two subjects experienced three SAEs (one subject with fatigue and head injury from fainting which resulted in hospitalization, and one subject with pneumonia). The SAEs of fatigue and pneumonia were classified as severe in intensity and the head injury was classified as mild. The subject who had fatigue and head injury continued treatment with minocycline foam, 4%. The subject who had pneumonia had already discontinued treatment (refer to the narrative below for more detail).

Overall, SAEs were uncommon during both the double-blind and open-label periods. There was no imbalance in SAEs between minocycline foam, 4% and vehicle during the double-blind period. Investigators considered none of the SAEs to be related to study drug.

Narrative summaries of subjects (treated with minocycline foam, 4% unless otherwise noted) who experienced SAEs are presented below:

Double-Blind Period

Trial FX2014-04

A 16 y/o female (Subject (b) (6)) with a history of acne, vasovagal syncope, cutting (since age 11), migraines, and depression ("sometimes" per subject) was admitted to the hospital after ingesting Benadryl, topiramate, Lasix, and ibuprofen in a suicide attempt on Day 78. She was hospitalized for 2 days before transfer to an inpatient psychiatric hospital. During the admission, she admitted to multiple psychosocial stressors including difficulty with relationships with parents and peers. She was discharged to home after 6 days in improved condition. The subject continued treatment with minocycline foam, 4%. The investigator classified the event as severe, the outcome resolved, and relationship to study drug unlikely.

Trial FX2014-05

A 21 y/o female (Subject (b) (6)) with a history of asthma experienced an exacerbation of asthma with hospitalization on Day 175. She was treated and discharged the following day with discharge medications including montelukast, prednisone, albuterol, and solumedrol. The subject continued treatment with minocycline foam, 4%. The investigator considered the event resolved on Day 82, of moderate severity, and relationship to study drug unlikely.

A 20 y/o female (Subject (b) (6)) with a history of gastric bypass surgery (4 months prior to study entry), "acid reflux," and constipation developed bowel obstruction causing bowel perforation on Day 9. She underwent emergency laparoscopic surgery to repair the perforation and was discharged to home after 6 days. The subject missed 2 doses of study drug but resumed and continued treatment. The investigator considered the events of bowel obstruction and perforation to be severe, resolved, and relationship to study drug unlikely.

A 15 y/o female (Subject (b) (6)) rolled from her bed onto the corner of a nightstand on Day 13. She was transported to the Emergency Department and was reportedly diagnosed with a broken nose by the Emergency Department physician. She was admitted to the hospital overnight for "precautionary monitoring." The subject continued treatment with minocycline foam, 4%. The investigator considered the event (preferred term facial bones fracture) mild in severity, ongoing, and not related to treatment.

A 24 y/o female (Subject (b) (6)) was discontinued from treatment with minocycline foam, 4% on Day 63 after a positive urine pregnancy test. The subject subsequently developed abdominal pain and presented to the hospital where she was diagnosed with a left sided isthmic ectopic pregnancy. A laparoscopic surgery with salpingectomy was performed. The investigator classified the event as severe, the outcome resolved, and relationship to study drug unlikely.

Trial FX2017-22

A 27 y/o female was discontinued from the study on Day 26 after a positive pregnancy test. The subject reported to the site that she had experienced a spontaneous abortion at home on Day 54. She was reportedly seen by her gynecologist confirmed that she miscarried the fetus at 6

weeks. The cause of the miscarriage is unknown. The investigator considered the event resolved, of mild severity, and the relationship to study drug as unlikely.

A 31 y/o female (Subject (b) (6)) randomized to vehicle began to have pelvic pain on Day 75 and visited her primary care physician on Day 77. Ultrasound and laboratory evaluations confirmed an SAE of spontaneous abortion. The subject was reportedly unaware of her pregnancy. The investigator considered the severity of the event moderate, the outcome resolved, and the relationship to study drug as unlikely.

Open-Label Period

A 26 y/o female enrolled in Trial FX2014-04 (Subject (b) (6)) began the open-label phase of the trial on Day 86 and was discontinued on Day 149. She informed the site that she was hospitalized for pneumonia on Day 175 and discharged on Day 179. She was reported treated with "IV meds." Hospital records were requested, but the subject was lost to follow-up. The investigator classified the event as severe and the relationship to study drug as unlikely. Although the subject was lost to follow-up, the investigator classified the event as resolved.

A 23 y/o female enrolled in Trial FX2014-05 (Subject (b) (6)) began the open-label phase of the trial on Day 93. Relevant concomitant medications include the following, all on Day 272: IV solutions and metoclopramide for vomiting, and ketorolac tromethamine for headache. On Day 277 she reportedly felt dizzy, fainted, and struck her head. She was reportedly admitted for overnight observation with a diagnosis of exhaustion. Despite multiple attempts to obtain the hospital records, the hospital stated that they did not have any records from the dates the subject said the events occurred. The subject continued treatment with minocycline foam, 4%. The investigator considered the events resolved as of Day 278, the severity of the head injury from fainting event as mild and the exhaustion event as severe, and the relationship to study drug as not related.

Phase 2 and Phase 1 Studies

No SAEs were reported during the Phase 2 or Phase 1 studies.

Dropouts and/or Discontinuations Due to Adverse Events

In the Phase 3 Primary Pool during the double-blind period, five subjects (5/1356; 0.4%) treated with minocycline foam, 4% and 8 (8/1058; 0.8%) subjects treated with vehicle discontinued from the trial due to AE. Of the five subjects who discontinued from minocycline foam, 4%, two discontinued due to SAEs; these included one subject with ectopic pregnancy and one with spontaneous abortion and were discussed in the previous section. Both events were considered unlikely related to treatment. The other three AEs leading to discontinuation were thought to be possibly or probably related to treatment. The TEAEs leading to discontinuation are summarized in Table 21 below.

Table 21: TEAEs Leading to Discontinuation During Double-Blind Period

Body System or Organ Class	Preferred Term	Minocycline Foam, 4% N=1356	Vehicle Foam N=1058
General disorders and administration site conditions	Application site acne	0 (0.0%)	1 (0.1%)
	Application site burn	0 (0.0%)	1 (0.1%)
	Application site erythema	0 (0.0%)	1 (0.1%)
	Application site pruritus	0 (0.0%)	1 (0.1%)
	Cyst	1 (0.1%)	0 (0.0%)
	Facial pain	1 (0.1%)	0 (0.0%)
	Nodule	0 (0.0%)	1 (0.1%)
Investigations	Hepatic enzyme increased	0 (0.0%)	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1 (0.1%)	1 (0.1%)
	Ectopic pregnancy	1 (0.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Hyperhidrosis	0 (0.0%)	1 (0.1%)
	Pruritus	1 (0.1%)	0 (0.0%)
	Rash generalized	0 (0.0%)	1 (0.1%)
	Skin hemorrhage	1 (0.1%)	0 (0.0%)
	Swelling face	1 (0.1%)	0 (0.0%)
	Yellow skin	1 (0.1%)	0 (0.0%)
	Subjects	5 (0.4%)	8 (0.8%)
	Events	8	9

Source: Reviewer's table created in JReview using ISS dataset
Abbreviation: TEAEs = treatment-emergent adverse events

Narratives of subjects treated with minocycline foam, 4% who discontinued due to TEAEs during the double-blind phase are presented below:

A 13 y/o male (Subject (b) (6)) experienced left sided facial pain and facial swelling beginning on Day 28. The drug was stopped on Day 31. The facial swelling resolved on Day 36 and the pain resolved on Day 37. He was discontinued from the study for these events on Day 42. The investigator considered the severity as moderate, the outcome resolved, and the relationship to study drug as possible.

A 20 y/o female (Subject (b) (6)) was treated from November 4, 2017 until February 24, 2018 (Day 113). On an unknown date in January 2018, she experienced facial skin bleeding and staining of skin yellow. She was discontinued from the study for these events on Day 113. The investigator considered the severity of the facial skin bleeding as mild and the staining of skin yellow as moderate and the outcome for both as resolved. The investigator considered the relationship to the study drug of the facial skin bleeding to be possible, and the staining of skin yellow to be probable.

An 18 y/o female (Subject (b) (6)) experienced cystic nodules and itching on Day 38. The last dose of study drug was administered on Day 37. She was discontinued from the study for these events on Day 59. The events were considered resolved the same day. The investigator considered the severity of the cystic nodules and itching as moderate, the outcome as resolved, and the relationship to study drug as probable.

During the open-label period of Trials FX2014-04 and FX2014-05, seven (7/657; 1.1%) of subjects discontinued due to AE. Details of these discontinuations are provided in Table 22 and Table 23 below.

Table 22: TEAEs Leading to Discontinuation during Open-Label Period Trial FX 2014-04

Site/Subject Number	Preferred Term	TEAE Start Day/ TEAE End Day	Severity/ Relationship/ Outcome	Action Taken/ Other Action Taken/ SAE? (Yes or No)
Double-Blind Treatment – FMX101 4%				
(b) (6)	Application Site Acne	197/--	Mild/ Possible/ Recovering/Resolving	Drug Withdrawn/ Discontinued Study/ No
Double-Blind Treatment – Vehicle Foam				
(b) (6)	Application Site Acne	197/--	Mild/ Possible/ Recovering/Resolving	Drug Withdrawn/ Discontinued Study/ No

TEAE = treatment-emergent adverse event
Notes: 1) TEAEs during the open-label period were defined as AEs starting on or after the first open-label application of study treatment; 2) Study day was calculated relative to the date of Day 1, the date of first study drug administration during the double-blind period.
Source: CSR FX2014-04, Data Listing 16.2.7.3.1

Table 23: TEAEs Leading to Discontinuation during Open-Label Period Trial FX 2014-05

Site/Subject Number	Preferred Term	TEAE Start Day/ TEAE End Day	Severity/ Relationship/ Outcome	Action Taken/ Other Action Taken/ SAE? (Yes or No)
Double-Blind Treatment – FMX101 4%				
(b) (6)	Application Site Edema	110/114	Moderate/ Possible/ Recovered/Resolved	Drug Withdrawn/ Discontinued Study/ No
(b) (6)	Abdominal Pain Upper	185/189	Mild/ Unlikely/ Recovered/Resolved	Drug Withdrawn/ Discontinued Study/ No
Double-Blind Treatment – Vehicle Foam				
(b) (6)	Flank Pain	92/107	Mild/ Unlikely/ Recovered/Resolved	Drug Withdrawn/ Discontinued Study/ No
(b) (6)	Abdominal Pain Upper	183/188	Mild/ Unlikely/ Recovered/Resolved	Drug Withdrawn/ Discontinued Study/ No
(b) (6)	Application Site Dermatitis	174/176	Mild/ Probable/ Recovered/Resolved	Drug Withdrawn/ Discontinued Study/ No

TEAE = treatment-emergent adverse event
Notes: 1) TEAEs during the open-label period were defined as AEs starting on or after the first open-label application of study treatment; 2) Study day was calculated relative to the date of Day 1, the date of first study drug administration during the double-blind period.
Source: CSR FX2014-05, Data Listing 16.2.7.3.1

Narratives for these subject are presented below:

Trial FX2014-04

A 13 y/o male (Subject (b) (6)) treated with minocycline foam, 4% during the double-blind phase began open-label treatment on Day 85. The subject experienced application site acne

(verbatim term “worsening acne”) beginning on Day 197 and discontinued treatment. The last dose of study drug was administered on Day 196. The investigator considered the severity of the event mild, the outcome as resolving, and the relationship to study drug as possible.

A 13 y/o female (Subject (b) (6)) treated with vehicle during the double-blind phase began open-label treatment with minocycline foam, 4% on Day 85. The subject experienced application site acne (verbatim term “worsening acne”) beginning on Day 197 and discontinued treatment. The last dose of study drug was administered on Day 196. The investigator considered the severity of the event mild, the outcome as resolving, and the relationship to study drug as possible.

Trial FX2014-05

A 17 y/o male (Subject (b) (6)) treated with minocycline foam, 4% during the double-blind phase began open-label treatment on Day 85. The subject experienced application site edema inside the treatment area with onset on Day 110. Study drug was discontinued, and the subject withdrew from the study. The event was reported as resolved on Day 114. The investigator considered the severity of the event moderate, the outcome as resolved, and the relationship to study drug as possible.

A 16 y/o female (Subject (b) (6)) treated with minocycline foam, 4% during the double-blind phase began open-label treatment on Day 92. The subject experienced upper abdominal pain beginning on Day 185. The subject was discontinued from the trial and study drug withdrawn on Day 188. The AE reportedly resolved on Day 189. The investigator considered the severity of the event mild, the outcome as resolved, and relationship to study drug as unlikely.

A 16 y/o male (Subject (b) (6)) treated with vehicle during the double-blind phase began open-label treatment with minocycline foam, 4% on Day 87. The subject experienced an AE of flank pain beginning on Day 92. Study drug was withdrawn, and the event resolved on Day 107. The investigator considered the severity of the event as mild, the outcome as resolved, and the relationship to study drug as unlikely.

A 34 y/o female (Subject (b) (6)) treated with vehicle during the double-blind phase began open-label treatment with minocycline foam, 4% on Day 91. The subject experienced upper abdominal pain beginning on Day 183. Study drug was withdrawn, and the subject was discontinued from the study with the last dose administered on Day 182. The event resolved on Day 188. The investigator considered the severity of the event as mild, the outcome as resolved, and the relationship to study drug as unlikely.

A 20 y/o male (Subject (b) (6)) treated with vehicle during the double-blind phase began open-label treatment with minocycline foam, 4% on Day 85. The subject experienced application site dermatitis inside the treatment area with onset on Day 165. Study treatment was interrupted, and the event resolved on Day 173. The subject again had application site dermatitis inside the treatment area with onset on Day 174. Study drug was withdrawn, and the subject was discontinued from the trial. The event was resolved on Day 176. The investigator considered the severity of the events as mild, the outcomes as resolved, and the relationship to study drug as probable.

Significant Adverse Events

Human Reproduction and Pregnancy

During the development program, females of childbearing potential were required to have a negative pregnancy test at screening and to use effective forms of contraception. In addition, UPTs were performed at Weeks 3, 6, 9, and 12 and final visit or when a subject prematurely withdrew from the study. For the open-label periods of Trial FX2014-04 and FX2014-05, subjects were provided with home pregnancy tests and instructed to test monthly and if a pregnancy was suspected between visits (e.g., if a subject missed her period). A UPT was also performed at Week 52/ final visit. If pregnancy was confirmed, the subject was withdrawn from the study and followed until the outcome of the pregnancy was known.

A total of 21 pregnancies were reported during the Phase 3 trials. The pregnancy outcomes and study treatment received were as follows:

- Nine healthy babies born (seven in minocycline foam, 4% group, two in vehicle group)
- One baby was born with minor abnormalities (underweight, hyperbilirubinemia of prematurity and treatment for hypoglycemia); minocycline foam, 4%
- Four spontaneous abortions (no other details available); (two each in minocycline foam, 4% and vehicle groups)
- Two elective abortions (no other details available); (1 each in minocycline foam, 4% and vehicle groups)
- One pregnancy complication requiring surgical intervention (laparoscopic salpingectomy-no other details available); minocycline foam, 4%
- Four cases - outcome is unknown at time of reporting, follow-up with these subjects is continuing to determine their pregnancy outcomes; (one in minocycline foam, 4% group, three in vehicle group)

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. 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 a review dated July 15, 2019, Dr. Liedtka provided labeling recommendations for Section 8.1 and 8.2 as well as the following comments:

Pregnancy

The application of topical minocycline resulted in measurable but very low concentrations of minocycline with a geometric mean AUC of 20.7 ng*hr/mL for adult subjects under maximal use conditions, and a geometric mean AUC of 46 ng*hr/mL for pediatric subjects treated under

maximal use conditions. After discussion with the DDDP pharmacology/toxicology team, DPMH agrees with the addition of the following statement in Section 8.1 of labeling: (b) (4) systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug."

DPMH had proposed to the division that, due to these very low levels, many of the "Warnings and Precautions" noted in labeling for the systemic formulation of minocycline might not be applicable to the topical treatment of acne with AMZEEQ. However, after internal discussion the division opted to maintain all the "Warnings and Precautions". The multiples of human exposure in the animal studies which showed some skeletal malformations ranged from approximately 250-650 times for the topical product.

Lactation

Minocycline is known to be excreted into human milk at low levels after oral administration. Given the low absorption of topical minocycline, and the fact that any minocycline that was excreted into breast milk after topical exposure would be likely to be complexed with the calcium in breast milk (therefore even further limiting the amount available for absorption from the infant's stomach), DPMH recommended that the Division consider using the risk/benefit statement in labeling for Section 8.2. DPMH also recommended removing the breastfeeding warning from the HPI for AMZEEQ.

However, the division was concerned that the exposure threshold is not known for the potential adverse effects of minocycline on the infant (tooth discoloration and inhibition of bone growth) and the consensus was that the risk of chronic low doses received while the mother is being treated topically outweighs the benefit received by treating acne with minocycline. The Division elected to keep the advice not to breastfeed for sub-Section 8.2.

(b) (4)

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events (TEAEs)

There were 345 (345/1356; 25.4%) subjects with treatment–emergent adverse events (TEAEs) in the minocycline foam, 4% group compared with 258 (258/1058; 24.4%) in the vehicle group. The most frequently reported TEAEs were in the system-organ class (SOC) of Infections and infestations. In this SOC, the most common preferred terms (PT) were "viral upper respiratory tract infection" and "upper respiratory tract infection."

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, the PT of Application site discoloration was reported by 5 (0.4%) of subjects in the minocycline foam, 4% group and 1 (0.1%) of subjects in the vehicle group. The rate of application site reactions was otherwise similar between treatment groups; such reactions were overall uncommon.

TEAEs by SOC are presented in order by descending frequency in Table 24 below.

Table 24: TEAEs by SOC in Descending Order by Frequency, Phase 3 Primary Pool

Body System or Organ Class	Minocycline Foam, 4% n=1356	Vehicle Foam n=1058
Infections and infestations	156 (11.5%)	115 (10.9%)
Skin and subcutaneous tissue disorders	44 (3.2%)	54 (5.1%)
Nervous system disorders	52 (3.8%)	38 (3.6%)
Investigations	37 (2.7%)	30 (2.8%)
Injury, poisoning and procedural complications	44 (3.2%)	22 (2.1%)
Respiratory, thoracic and mediastinal disorders	30 (2.2%)	34 (3.2%)
Gastrointestinal disorders	31 (2.3%)	19 (1.8%)
General disorders and administration site conditions	30 (2.2%)	13 (1.2%)
Musculoskeletal and connective tissue disorders	19 (1.4%)	8 (0.8%)
Psychiatric disorders	8 (0.6%)	5 (0.5%)
Blood and lymphatic system disorders	7 (0.5%)	5 (0.5%)
Ear and labyrinth disorders	6 (0.4%)	4 (0.4%)
Reproductive system and breast disorders	5 (0.4%)	4 (0.4%)
Eye disorders	3 (0.2%)	4 (0.4%)
Immune system disorders	5 (0.4%)	2 (0.2%)
Metabolism and nutrition disorders	6 (0.4%)	1 (0.1%)
Renal and urinary disorders	2 (0.1%)	2 (0.2%)
Hepatobiliary disorders	2 (0.1%)	2 (0.2%)
Vascular disorders	4 (0.3%)	0 (0.0%)
Pregnancy, puerperium and perinatal conditions	2 (0.1%)	1 (0.1%)
Surgical and medical procedures	2 (0.1%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl.cysts and polyps)	3 (0.2%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	1 (0.1%)
Endocrine disorders	1 (0.1%)	0 (0.0%)

Source: Reviewer's Table from JReview using ISS Dataset
Abbreviations: TEAE = treatment-emergent adverse event; SOC = system-organ class

Treatment-Emergent Adverse Events by Severity

Most TEAEs were mild or moderate in severity. Eight (8/1356; 0.6%) of subjects in the minocycline foam, 4% group experienced 10 severe TEAEs; five (5/1058; 0.5%) of subjects in the vehicle group experienced seven severe TEAEs. The only treatment-related severe TEAEs in the minocycline foam, 4% group occurred in a 12-year-old white female of Latino ethnicity (Subject FX2017-22-(b) (6)) who experienced yellow skin beginning on Day 1. Although the investigator assessed the AE as severe, probably related to treatment, and the AE was ongoing, the subject completed the Trial. No further information was provided regarding this subject. One subject in the vehicle group experienced a severe TEAE of nodule which the investigator assessed as possibly related to treatment; treatment was withdrawn for this subject. Severe TEAEs that were considered serious included suicide attempt, intestinal

obstruction/perforation, ectopic pregnancy, cholecystitis/gastritis, esophageal stenosis, and intestinal obstruction/ enteritis. These are discussed in the previous subsection of this review.

Severe TEAEs are presented by SOC and PT in Table 25 below.

Table 25: Severe TEAEs by SOC and PT, Phase 3 Primary Pool

Body System or Organ Class	Preferred Term	Minocycline Foam, 4% n=1356	Vehicle Foam n=1058
Gastrointestinal disorders	Intestinal obstruction	1 (0.1%)	1 (0.1%)
	Intestinal perforation	1 (0.1%)	0 (0.0%)
	Vomiting	1 (0.1%)	0 (0.0%)
Infections and infestations	Gastroenteritis viral	1 (0.1%)	0 (0.0%)
	Tooth abscess	1 (0.1%)	0 (0.0%)
Metabolism and nutrition disorders	Dehydration	1 (0.1%)	0 (0.0%)
Nervous system disorders	Headache	1 (0.1%)	0 (0.0%)
Pregnancy, puerperium and perinatal conditions	Ectopic pregnancy	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Suicide attempt	1 (0.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Yellow skin	1 (0.1%)	0 (0.0%)
Gastrointestinal disorders	Enteritis	0 (0.0%)	1 (0.1%)
	Gastritis	0 (0.0%)	1 (0.1%)
	Esophageal stenosis	0 (0.0%)	1 (0.1%)
General disorders and administration site conditions	Nodule	0 (0.0%)	1 (0.1%)
Hepatobiliary disorders	Cholecystitis	0 (0.0%)	1 (0.1%)
Infections and infestations	Otitis media	0 (0.0%)	1 (0.1%)
	Subjects	8 (0.6%)	5 (0.5%)
	Events	10	7

Source: Reviewer's Table from JReview using ISS Dataset
Abbreviations: TEAE = treatment-emergent adverse event; SOC = system -organ class; PT = preferred term

TEAEs during the Open-Label Period of Trials FX2014-04 and FX2014-05

TEAEs during the open-label periods of Trials FX2014-04 and FX2014-05 were reported for each trial individually rather than as pooled data. During the open-label period of Trial FX2014-04, the TEAEs and frequency at which the events occurred was similar to that of the Phase 3 Primary Pool. During the open-label period of Trial FX2014-05, the TEAEs and frequency at which the events occurred was similar to that of the Phase 3 Primary Pool, except for headache. Headache was reported in 17/362 (4.7%), compared to 2.9% in the Phase 3 Primary Pool. Overall, data from the open-label periods was sufficient to demonstrate the long-term safety of minocycline foam, 4% for up to 1 year.

Adverse Reactions

A total of 41 (3.0%) subjects in the minocycline foam, 4% group and 38 (3.6%) of subjects in the vehicle group experienced TEAEs assessed by the Applicant as treatment-related (i.e., AR). The Applicant proposed to include the following statement in Section 6 (Adverse Events) in product labeling: "The most common adverse reactions reported during clinical trials were upper

respiratory tract infection, headache, elevated blood creatine phosphokinase (CPK) and acne." These AE are displayed in Table 26 below in decreasing order by frequency of occurrence in the minocycline foam, 4% group.

Table 26: Adverse Reactions Proposed by Applicant for Labeling in Descending order by Frequency in Minocycline Foam Group

Adverse Reaction	Minocycline Foam, 4% (N=1377)	Vehicle Foam (N=1068)
Upper respiratory infection[1]	82 (6.0%)	65 (6.1%)
Headache[2]	40 (2.9%)	26 (2.5%)
Blood creatine phosphokinase increased	24 (1.8%)	14 (1.3%)
Acne	22 (1.6%)	26 (2.5%)

Source: Reviewer's Table from JReview using ISS Dataset
[1] Upper Respiratory Infection includes upper respiratory tract infection (URTI), viral URTI, nasopharyngitis, pharyngitis, and viral pharyngitis
[2] Headache includes headache and tension headache

In order to better characterize the frequency of upper respiratory infections, we pooled the clinically related PTs of upper respiratory tract infection (URTI), viral URTI, nasopharyngitis, pharyngitis, and viral pharyngitis. After pooling, the frequency is similar between treatment groups which makes a relationship of URTI to treatment unlikely. Therefore, we do not recommend inclusion of URTI in the Adverse Events Section of product labeling.

In order to better characterize the frequency of headaches, we pooled the clinically related PTs of headache and tension headache. The Applicant provided no alternative explanation for the observed imbalance in headaches between treatment groups. Headache is also listed in Section 6 (Adverse Reactions) in labeling for the listed drug, SOLODYN®. We agree with the Applicant's proposed inclusion of headache under Adverse Reactions in labeling.

The imbalance in frequency of elevated CPK levels was relatively small, with a difference between minocycline foam, 4% and vehicle of only 0.5%. CPK levels transiently rise after exercise or heavy manual labor. A review of the literature revealed that the distribution of CPK levels in a healthy population is thought to be skewed toward higher values than those currently considered normal. Because of this, the European Federation of Neurological Societies suggests redefining elevated CPK as values 1.5 times beyond the upper limit of normal. [9] Of the 24 subjects in the minocycline foam, 4% group with elevated CPK, 11 subjects had CPK levels less than three times the current upper limit of normal. We reviewed narratives for six subjects with the highest CPK values (>5 times the upper limit of normal); all had plausible alternative explanations (mostly vigorous physical activity). The Applicant considered the majority of elevated CPK events to be unlikely related to treatment. Elevated CPK is not mentioned in Section 5 (Warnings and Precautions) or Section 6 (Adverse Reactions) in labeling for SOLODYN®. We concluded that the imbalance in elevated CPK between groups is not related to treatment and we do not recommend inclusion of elevated CPK in Section 6 (Adverse Reactions) in product labeling.

[9] Moghadam-Kia, S, C Oddis, and R Aggarwal, 2016, Approach to Asymptomatic Creatine Kinase Elevation, Cleve Clin J Med, 83(1): 37–42

Although acne was reported as an adverse event in 1.6% of subjects in the minocycline foam, 4% group, it was reported in 2.5% of subjects in the vehicle group. In this setting, acne more likely represents treatment failure rather than an adverse reaction to treatment. For these reasons, we do not recommend inclusion of acne in Section 6 (Adverse Events) in 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 AMZEEQ and more frequently than vehicle was headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle."

Laboratory Findings

The Applicant reported that mean changes from baseline in serum chemistry and hematology laboratory parameters were similar across treatment groups and timepoints. The majority of shifts in laboratory test results remained within normal range at the baseline and post-baseline (Week 3 and Week 12) timepoints. Elevations in CPK are discussed in the previous subsection.

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 reviewed AE PTs associated with hepatotoxicity, including Alanine aminotransferase increased, Blood bilirubin increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Gamma-glutamyl transferase increased, and Liver function test increased. 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). In the Phase 3 Primary Pool, there were no clinically meaningful changes in BUN at Week 3 and Week 12.

Open-Label Period

The Applicant reported no notable mean changes were observed in hematology, serum chemistry, or urinalysis parameters during the open-label period in Study FX2014-04. A total of 12 (12/284; 4.2%) subjects had abnormal laboratory results that were considered clinically significant and recorded as AEs; most resolved during the study. The only TEAEs associated with abnormal laboratory results that were not resolved included one subject with low glucose and 1 with decreased white blood cell count.

The Applicant reported no notable mean changes were observed in hematology, serum chemistry, or urinalysis parameters during the open-label period in Study FX2014-05. A total of 19 (19/373; 5.1%) subjects had abnormal laboratory results that were considered clinically significant and recorded as AEs; most resolved during the study. One subject had two TEAEs associated with abnormal laboratory results that were not resolved; these were bilirubin conjugated and blood phosphorus increased. Investigators considered both events unlikely related to study treatment.

Vital Signs

In the Phase 3 Primary Pool, vital signs (blood pressure and heart rate) were assessed during clinic visits at Weeks 1, 3, 6, 9, and 12. During the open-label period of Trials FX2014-04 and FX2014-05, subjects returned for visits at Week 16, then every 6 weeks until Week 52.

The Applicant reported that overall mean changes from baseline in vital signs are similar across treatment groups.

Only one AE related to vital signs was reported during the Phase 3 Trials. Tachycardia was reported in one subject (1/1058; 0.1%) in the vehicle group. Otherwise, no individual vital sign finding was considered clinically significant by the investigators during the double-blind and open-label periods of the Phase 3 trials.

Electrocardiograms (ECGs)/ QT

The Applicant performed ECGs on a total of 18 subjects (age 39 years and older only) treated with minocycline foam, 4% in Phase 3 Trials FX2014-04 and FX2014-05. There were no clinically significant abnormalities. In the Summary of Clinical Safety, the Applicant provided a risk assessment of the proarrhythmic potential of minocycline foam, 4%. 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, 4% 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.

8.2.5. Analysis of Submission-Specific Safety Issues

Minocycline is an antibiotic in the tetracycline class and is available in oral and IV formulations. There are no formulations of minocycline for topical administration approved in the United States. 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, 4% 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, investigators assessed local skin tolerability (erythema, dryness, hyperpigmentation, and skin peeling at the sites of study drug application) at each visit on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Itching was assessed using the same scale based on the subjects' subjective assessment. Most subjects had scores of 0 (none) for all local tolerability parameters at Week 1 and Week 12. Local tolerability findings at Week 12, based on our analyses, are presented in Table 27 below.

Table 27: Local Tolerability at Week 12 in the Phase 3 Trials

Parameter	AMZEEQ (n=1166)*	Vehicle Foam (n=877)*
Erythema	183 (15.7%)	146 (16.6%)
Hyperpigmentation	180 (15.4%)	142 (16.2%)
Dryness	84 (7.2%)	91 (10.4%)
Itching	69 (5.9%)	61 (6.9%)
Peeling	39 (3.3%)	43 (4.9%)

Source: Reviewer's Table created in JReview using ISS dataset
* 190 subjects in the AMZEEQ group and 181 subjects in the Vehicle group had missing local tolerability assessments at Week 12

Most of the local tolerability findings were mild in severity. Investigators characterized the hyperpigmentation as being characteristic of inflammatory and post-inflammatory changes associated with acne. 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):

> Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. Table 1 presents the active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ.

Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ.

Table 28: Facial Cutaneous Tolerability Assessment

	AMZEEQ, % (N=1,377)		
Symptom/Severity	Mild	Moderate	Severe
Erythema	14.2	1.5	0
Dryness	6.8	0.6	0
Hyperpigmentation*	12.4	2.8	0.1
Skin Peeling	3.2	0.2	0
Itching	5.1	0.8	0.1

*Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne.

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

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 (UV) 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 3 trials, investigators advised subjects to "refrain from excessive sun exposure and tanning booths for the duration of the stud(ies)". We analyzed AE data from the Phase 3 trials for preferred terms (PT) associated with photosensitivity. The only PT associated with photosensitivity during the double-blind period was "sunburn", which was reported by 4/1356 (0.3%) of subjects in the minocycline foam, 4% and 2/1058 (0.2%) in the vehicle group. During the Open-Label Period, no subjects reported AEs related to photosensitivity in Trial FX2014-04 and "sunburn" was reported by 1/343 (0.3%) of subjects in Trial FX2014-05.

The Applicant also conducted provocative dermal safety studies to evaluate the phototoxicity and photoallergenicity potential of minocycline foam, 4%. 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, 4%.

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 preferred terms (PT) associated with CNS effects. During the double-blind period of the Phase 3 trials, the PT "dizziness" was reported by 2/1356 (0.1%) of subjects in the minocycline foam, 4% group and 1/1058 (0.1%) in the vehicle group. In addition, the PT of "syncope" was reported by 2/1356 (0.1%) of subjects in the minocycline foam, 4% group and 3/1058 (0.3%) in the vehicle group. The PTs of "vertigo" and "vertigo positional" were each reported by 1/1058 (0.1%) in the vehicle group, but no subject in the minocycline foam, 4% group reported these AE. During the Open-Label Period, no subjects in Trial FX2014-04 reported any of these AEs; in Trial FX2014-05 "vertigo" was reported by 2/343 (0.6%) of subjects, "dizziness" by 1/343 (0.3%), and "syncope" by 9/343 (0.9%).

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, 4%.

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 3 trials. However, during the double-blind period of the Phase 3 trials, the PT of "hypersensitivity" was reported by 1/1356 (0.1%) subject in the minocycline foam, 4% group and no subjects in the vehicle group. In addition, the PT of "urticaria" was reported by 1/1356 (0.1%) of subjects in the minocycline foam, 4% group and 2/1058 (0.2%) of subject in the vehicle group. During the Open-Label Period, no subjects in Trial FX2014-04 reported any AE related to systemic hypersensitivity; in Trial FX2014-05, the PT "urticaria" was reported by 1/343 (0.3%) of subjects.

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, 4%.

Conclusion

During the development program for minocycline foam, 4% 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 the events listed in Section 5 (Warning and Precautions) for SOLODYN® to be included in labeling for minocycline foam, 4%.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Phase 3 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, 4% in different populations. Because the trials were not powered for these analyses, the data must be interpreted with caution. In subjects treated with minocycline foam, 4%, the adverse reaction (AR) of headache was reported more commonly in adult subjects (4.1%) than in pediatric subjects (0% in subjects aged 9 years to 11 years and 2% in subjects aged 12-17 years). Headache was also reported more frequently in female (2%) than male subjects (0.9%) treated with minocycline foam, 4%. Otherwise, there were no substantial differences in the risk of ARs in demographic subgroups.

We noted some minor demographic differences in the common TEAEs of pooled upper respiratory infections (URI) (which includes the following PTs: upper respiratory tract infection (URTI), viral URTI, nasopharyngitis, pharyngitis, and viral pharyngitis as described in Section 8.2.4 of this review). URI occurred more commonly in subjects treated with minocycline foam, 4% than vehicle in each of the pediatric age groups. In subjects aged 9 years to 11 years, pooled URI occurred in 5/23 (21.7%) of subjects treated with minocycline foam, 4% and 1/19 (5.3%) of subjects treated with vehicle. In subjects aged 12 years to 17 years, pooled URI occurred in 42/648 (6.5%) of subjects treated with minocycline foam, 4% and 27/496 (5.4%) of subjects treated with vehicle. However, this is consistent with the epidemiology of infections of this type and we conclude the imbalance is not related to treatment with minocycline foam, 4%. In subjects treated with minocycline foam, 4%, pooled URI also occurred more frequently in

female than in male subjects and in subjects of White race than in subjects of Non-White race. The frequency of reporting for other adverse events was similar between the demographic groups. Refer to Appendix 19.5 for a tabulated summary of treatment-emergent adverse reactions (TEARs) in demographic subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety data from a Phase 2 dose-ranging trial, two pharmacokinetics (PK) studies conducted under conditions of maximal use, and four provocative dermal safety studies. Safety results from these studies will be summarized briefly below.

Phase 2 Trial FX2010-03

This was a Phase 2, prospective, multicenter, randomized, double-blind, vehicle-controlled, parallel group, dose finding clinical trial, designed to evaluate the safety, tolerability and efficacy of FXFM244 antibiotic foam topical application for treatment of moderate to severe acne vulgaris (AV). FXFM244 contains the same active ingredient and excipients as the to-be-marketed formulation, except for silicon dioxide at 0.25% wt/wt which was not included in the to-be-marketed formulation.

The trial enrolled 150 subjects ages 12 years to 25 years of age with moderate to severe AV defined as:

- A minimum of 20 but not more than 50 inflammatory lesions on the face (papules and/or pustules).
- A minimum of 25 but not more than 100 noninflammatory lesions on the face (open and/or closed comedones).
- No significant nodulocystic acne on the face (≤2 lesions).
- A score of ≥3 (moderate or severe) on the IGA scale

Subjects were randomized 1:1:1 to one of three treatments:

- FXFM244 1%
- FXFM244 4%
- Vehicle foam

Subjects applied the assigned product to affected areas once daily in the evening for 12 weeks before entering a 4-week Follow-Up Period. The evaluation of safety included the following:

- Adverse events (AEs)
- Physical examination
- Vital signs (blood pressure, heart rate, and oral body temperature)
- Concomitant medications reported using the generic name
- Local tolerability assessment: Clinical assessment of skin irritation (erythema, dryness, pigmentation, peeling, and itching) using a scale of 0 to 3

Safety Results

A total of 139 subjects completed the trial. No deaths or serious AE (SAE) were reported. Five (5/139; 3.6%) of subjects reported five TEAEs. TEAEs included laryngitis and erosion of the lip in the FXFM244 4% group, two AEs of scratching the nose skin (1 in the FXFM244 1%, and 1 in the Vehicle group), and one subject each with herpes simplex of the nose and forehead injury in the Vehicle group. All were mild in severity and all resolved except for the subject with acute laryngitis, who was treated with oral antibiotics. None of these AEs resulted in discontinuation from the study.

One subject was discontinued because of pregnancy. The pregnancy outcome was uneventful, and the subject delivered twins at 38 weeks gestation. The infants were of "normal weight"; no further information was provided.

The Applicant reported that there were no clinically or statistically significant differences between treatment groups in the active assessment of local tolerability. Most cases of erythema, skin dryness, change in pigmentation and skin peeling were mild, sporadic and transient, with most occurring at Visit 2 (Week 3) post-baseline. No itching was observed at any study visit.

Maximal Use PK Studies

Study FX2014-03

This Phase 1 study 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 enrolled 30 subjects age 18 years to 35 years with moderate to severe AV.

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)
- 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 29 below.

Table 29: 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)

Source: FX2014-03 CSR, Table 12-2, p,.48
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

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.

Study FX2016-21

This was a single-center, nonrandomized, open-label study to evaluate multiple dose topical administration of minocycline foam, 4% in pediatric subjects ages 9 years to 16 years 11 months under conditions of maximal use. The study enrolled 20 subjects with moderate to severe AV: 6 in Cohort 1 (age 9 years to 11 years), 8 in Cohort 2 (age 12 years to 14 years), and 6 in Cohort 3 (age 15 years to 16 years 11 months). Subjects applied 4 grams of minocycline foam, 4% once daily for 7 days to the face, neck, upper chest, shoulders, and upper arms and back. All subjects completed the study.

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)
- Pregnancy testing
- Vital signs
- Physical examination

Safety Results

No deaths, SAEs, or severe TEAEs were reported; no subjects discontinued or required a reduction in dose because of an AE. One subject (1/20; 5%) reported two TEAEs (nausea and vomiting). Both were moderate in intensity and considered not related to treatment. There were no clinically significant abnormalities in vital signs, physical examination, 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 foam, 4%. The trials evaluated the potential of minocycline foam, 4% for sensitization, irritation, phototoxicity, and photoallergenicity. The results are presented below.

Trial FX2016-07 (Sensitization)

This was a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the investigational products (IPs) (minocycline foam, 4% and vehicle foam), as well as positive and negative controls under occlusive conditions in healthy adult volunteer subjects.

The safety population included 233 subjects, the cumulative irritancy population included 218 subjects, and the sensitization population included 213 subjects. Each subject received 10 applications of each of the following:

- Minocycline foam, 4%
- Vehicle foam
- Sodium lauryl sulfate (SLS), 0.2% (positive control)
- 0.9% saline (negative control)

During the Induction Phase of the study, the IPs and controls were applied to adjacent sites on the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. A total of 10 patch applications were made over a period of approximately 6 to 8 weeks.

Following the Induction Phase, subjects had a 10 to 14-day Rest Period, after which they entered the Challenge Phase, which consisted of one 48-hour patch application to a naive site on the opposite side of the back. Observations at the naive site during Challenge Phase and the patterns of reactivity during the Induction Phase provided a basis for an interpretation of contact sensitization.

Investigators assessed the patch sites at baseline (Day 1), nine times during the Induction Phase, and four times during the Challenge Phase and graded the response using the following scales as in Table 30 and Table 31:

Table 30: Response Symbols and Numerical Equivalents

Grade	Definition	Score*
0	No evidence of irritation	0
1	Minimal erythema; barely perceptible	1
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	2
3	Erythema and papules	3
4	Definite edema	3
5	Erythema, edema, and papules	3
6	Vesicular eruption	3
7	Strong reaction spreading beyond test site	3

Source: FX2016-07 CSR, Table 9-3, p.25
* Scores were utilized only during the statistical analysis process of the study. Grades were conducted throughout the study by the clinical staff.

Table 31: Effect on Superficial Layers of the Skin

Symbol	Grade	Response
A	0	Slight glazed appearance
C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch
H	3	Small petechial erosions and/or scabs

Source: FX2016-07 CSR, Table 9-4, p.25

Results:

During the Challenge Phase, no subjects showed evidence of contact sensitization to any of the products applied. No rechallenge was necessary for this study. The investigators also conducted assessments of cumulative irritation. Minocycline foam, 4%, vehicle foam, and 0.9% saline showed no significant irritation; SLS 0.2% had higher mean cumulative irritation and total irritation scores.

Thirteen subjects had a total of 16 AEs. There were no deaths or SAEs. One (1/233; 0.4%) subject had a TEAE leading to withdrawal (an episode of syncope on Day 5 that was moderate

in severity, resolved the same day, and was considered unrelated to treatment). AEs reported by more than one subject included nasal congestion in 5 (5/233; 2.1%) subjects, and oropharyngeal pain and cough, occurring in 2 (2/233; 0.9%) subjects each. All AEs were mild or moderate in severity; investigators considered none of the AE to be treatment-related.

Trial FX2016-08 (Cumulative Irritant Patch Test)

This was a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the investigational products (IPs) (minocycline foam, 4% and vehicle foam), as well as positive and negative controls under occlusive conditions in healthy volunteer subjects.

A total of 42 subjects were randomized and 39 completed the trial. None of the three subjects who discontinued did so because of an AE. Each subject received applications of each of the following:

- Minocycline foam, 4%
- Vehicle foam
- Sodium lauryl sulfate (SLS), 0.2% (positive control)
- 0.9% saline (negative control)

The IPs and controls were applied once daily for 21 days under occlusion to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. Investigators used the same scales as those for Trial FX2016-08 which are displayed in the tables above. Other notations could be made in place of a score to designate particular circumstances preventing the assignment of a score or in addition to a score to identify damage to the epidermis and/or spreading of a reaction beyond the patch site. These are presented in Table 32 below.

Table 32: Other Notations Used in the Cumulative Irritation Trial

Notation	Definition
X	Subject absent
B	Burning or stinging sensation
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation
I	Itching
D	Damage of the epidermis: oozing, crusting, and/or superficial erosions
p	Papular response
pv	Papulovesicular response
S	Spreading of reaction beyond patch site (i.e., reaction where study material did not come in contact with skin)
T	Tape related reaction

Source: FX2016-08 CSR, Table 9-5, p. 24

Results

Mean irritation scores for the IPs and controls were as follows: minocycline foam, 4% 0.05, vehicle foam 0.04, 0.9% saline 0.13, and SLS 0.2% 2.14. The differences between minocycline foam, 4%, vehicle foam, and saline were not statistically significant. The differences between the scores for positive control SLS 0.2% and the IPs and 0.9% saline control was statistically significant (i.e., SLS 0.2% was more irritating).

Total irritation scores for the IPs and controls were as follows: minocycline foam, 4% 0.95, vehicle foam 0.79, 0.9% saline 2.79, and SLS 0.2% 44.92. The differences between minocycline foam, 4%, vehicle foam, and saline were not statistically significant. The differences between the scores for positive control SLS 0.2% and the IPs and 0.9% saline control was statistically significant (i.e., SLS 0.2% was more irritating). In addition, the patch discontinuation rate for SLS 0.2% was significantly higher than that for the IPs and 0.9% saline control.

Three subjects (3/42; 7.1%) experienced three AEs of fatigue that were mild in severity, did not result in discontinuation, and resolved. Investigators considered these AE unlikely related to treatment.

Trial FX2016-06 (Phototoxicity)

This was a single-center, controlled, randomized, within-subject comparison study of the investigational product minocycline foam, 4% and vehicle foam under occlusive patch conditions.

A total of 32 subjects were randomized and 31 completed the study. One subject did not return for the final visit and was discontinued. Each subject had an area (approximately 50 cm^2) defined on the infrascapular region of the back irradiated to determine the minimal erythemal dose of UV light. A total of 8 application sites (2 cm x 2 cm each) were marked on the subject's back. Minocycline foam, 4% and vehicle foam were applied in four sets (A, B, C, and D) at the application sites. One set of sites was irradiated at approximately 3 hours +/- 15 minutes post patch application, one set at approximately 24 hours post patch application, and two sets were not irradiated.

Subjects had patches applied on the infrascapular region of the back designated for test sample application and irradiation. The products were applied to the assigned sites under occlusive patch conditions. At approximately 3 hours +/- 15 minutes post patch application, the designated sites were exposed to irradiation. The irradiated sites and non-irradiated sites were examined for dermal reactions at approximately 21, 45, 69 and 93 hours. At approximately 24 hours post patch application, the designated sites were exposed to irradiation. The irradiated sites and non-irradiated sites were examined for dermal reactions at approximately 24, 48, and 72 hours. Dermal reactions at the test sites were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation using the scales presented in Table 33 and Table 34 below:

Table 33: Grading of Responses

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1.0
Moderate erythema	++	2.0
Marked/severe erythema	+++	3.0
Edema		
Mild, but definite edema	**	1.0[1]
Definite edema with erosion/vesiculation	***	1.5

Source: FX2016-06 CSR, Table 9-3, p.29
[1] For data entry purposes, "0" was used to indicate no edema.

Table 34: Response Notations

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	p
Papulovesicular response	pv
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP

Source: FX2016-06 CSR, Table 9-4, p.30

Results

There were no statistically significant differences in irritation observed among the irradiated product sites and no statistically significant differences in irritation observed among the non-irradiated product sites. Investigators found no evidence of phototoxicity among the subjects in this trial. No TEAEs were reported during this trial.

Trial FX2016-09 (Photoallergenicity)

This was a single-center, controlled, randomized, within-subject comparison study of the investigational product minocycline foam, 4% and vehicle foam under occlusive patch conditions.

A total of 56 subjects were randomized and completed the Induction Phase; 55 subjects completed the Challenge Phase. One subject was discontinued because of an AE, which is discussed in more detail below. Subjects had 4 application sites (2 irradiated and 2 non-irradiated) on the infrascapular region of the back designated for test sample application and irradiation (if applicable). Minocycline foam, 4% and vehicle foam was applied to the assigned

sites under occlusive patch conditions. After approximately 24 +/-4 hours, the designated sites were exposed to irradiation. These procedures were performed twice weekly over a 3-week Induction Phase (6 applications/irradiations). The sites were examined at various time points for the purpose of determining photoallergic skin reactions. Dermal reactions at the test sites were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation using the same scales as those used in Trial FX2016-06, which are displayed in the tables above.

Results

The mean irritation scores for minocycline foam, 4% were 0.54 at the irradiated site and 0.00 at the non-irradiated site. The mean irritation scores for vehicle foam were 0.65 at the irradiated site and 0.00 at the non-irradiated site. For the pairwise comparisons for local tolerability during induction, there were statistically significant differences between irradiated and non-irradiated sites for both study products. The post-irradiation scores were mild and consistent with the irradiated control. Investigators concluded that the mild reaction was normal in response to UV light.

The criteria for photosensitization were not met for any study product, i.e., no subjects were sensitized to any study product. Investigators found no evidence of photoallergy among the subjects in this trial.

A total of five subjects (5/56; 8.9%) experienced AEs. All were mild or moderate in severity, and 4 of 5 resolved with no change in treatment (cold symptoms in two subjects, stiff neck, and paresthesia of lower right thigh). One subject was discontinued because of an AE of cold urticaria on the lower back. Investigators considered none of the AEs to be related to treatment.

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. However, no malignant neoplasms were reported during the Phase 3 trials.

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.

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

The Applicant evaluated pediatric subjects ages 9 to 17 years in the clinical trials which were the primary source of data to support the safety and efficacy of minocycline foam, 4% for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. These included Phase 3 trials FX2014-04, FX2014-05, FX2017-22; Phase 2 Trial FX2010-03 (ages 12 years and older); and Trial FX2016-21, which was a 7-day PK trial conducted under conditions of maximal use. The Phase 3 Primary Pool enrolled a total of 1180 (1180/2414; 48.9%) pediatric subjects; 123 (5.1%) were ages 9 years to 12 years and 1057 (43.8%) were ages 13 years to 17 years. A total of 666 of the pediatric subjects in the Phase 3 Primary Pool were treated with minocycline foam, 4%. In the maximal use PK study, an additional 20 subjects age 9 to <17 years were treated with minocycline foam, 4%.

The proposed product is a new dosage form of minocycline foam, 4%. On this basis, approval of this product for the treatment of acne vulgaris triggers the Pediatric Research Equity Act (21 U.S.C.355c).

Pediatric Study Plan

The Applicant submitted an initial Pediatric Study Plan (iPSP) on May 23, 2016. The Agency sent a Written Response on August 1, 2016, and the Applicant submitted an Agreed iPSP on October 31, 2016. The agency sent a letter verifying agreement with the Agreed iPSP on November 28, 2016. The Applicant requested a partial waiver of the requirement to conduct studies in subjects ages 0 to 8 years of age.

NDA Submission

In the NDA submission, the Applicant included a request to waive the requirement to conduct clinical studies with minocycline foam, 4% in the pediatric population from 0 to 8 years of age. The justification for waiving the required pediatric assessment was that the product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested, specifically:

> "The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used during tooth development."

The Applicant did not request a deferral because the Phase 2 and Phase 3 trials included the target pediatric population. In addition, the Applicant conducted a PK study under conditions of

maximal use in the target pediatric population. The Pediatric Review Committee (PeRC) "agreed with the Division to grant a partial waiver of pediatric studies for birth to less than 8 years of age and that this product has been assessed for pediatrics 9 years and older. Labeling will be updated to reflect the assessment for use in pediatric patients ages 9 years and older" (PeRC Meeting Minutes dated August 7, 2019). Therefore, the Agency will not require postmarketing assessments under the Pediatric Research Equity Act.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Per the Applicant, no overdoses occurred in the minocycline foam, 4% acne vulgaris clinical program. There is no information available on overdose with minocycline foam, 4%.

Drug Abuse Potential/ Withdrawal and Rebound

In view of the mechanism of action and low systemic exposure, there is no reason to anticipate any potential for abuse or dependency. The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. Therefore, the review team did not consult with the Controlled Substance Staff.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Minocycline foam, 4% 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, 4% 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, 4% in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile for minocycline foam, 4% was adequately characterized during the drug development program. The primary safety database consisted of 2414 subjects from Phase 3 trials FX2014-04, FX2014-05, and FX2017-22 (the Phase 3 Primary Pool). The safety population included all randomized subjects who received at least one dose of the study medication during double-blind treatment in the three Phase 3 studies and was analyzed according to the treatment that subjects received.

Review of the safety data did not reveal any contraindications to treatment with minocycline foam, 4%. Section 4 (Contraindications) will include only hypersensitivity to any of the tetracyclines or any of the ingredients within minocycline foam, 4%. Although systemic exposure from topical administration of minocycline foam, 4% 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 as class labeling in labeling for minocycline foam, 4%.

Treatment with minocycline foam, 4% was not associated with an increased risk of mortality or serious adverse events (SAEs). There were no deaths in the development program and there were no SAEs considered by investigators as related to treatment with minocycline foam, 4% or vehicle. In the Phase 3 Primary Pool, SAEs occurred in 0.4% of subjects in the minocycline foam, 4% group and in 0.5% of subjects in the vehicle group. During the double-blind Period of the Phase 3 trials the following SAEs occurred. Among subjects in the minocycline foam, 4% group, SAEs included ectopic pregnancy, spontaneous abortion, facial bones fracture, intestinal perforation and intestinal obstruction (same subject), suicide attempt, and asthma; each occurring in one subject. Among subjects in the vehicle group, SAEs included spontaneous abortion, intestinal obstruction, enteritis, gastritis, esophageal stenosis, cholecystitis, and biliary dyskinesia; each occurring in one subject (subjects may have had more than one SAE). During the open-label periods of Trials FX2014-04 and FX2014-05, one subject had an SAE of pneumonia and one subject had SAEs of head injury and fatigue. Investigators considered none of these SAEs related to treatment with minocycline foam, 4%.

The most common adverse reaction (AR) was headache, which was reported in 3% of subjects treated with minocycline foam, 4% and 2% of subjects treated with vehicle. The Applicant also conducted active assessments of local tolerability, the results of which were as follows at Week 12: erythema (15.7%), hyperpigmentation (15.3%), dryness (7.4%), itching (6.0%), and peeling (3.4%). Investigators characterized the hyperpigmentation as being characteristic of inflammatory and postinflammatory changes associated with acne. Most local tolerability adverse reactions were mild in severity and occurred with similar frequency as subjects treated with the vehicle component of minocycline foam, 4%. This information will be included in Section 6 (Adverse Reactions) in product labeling.

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. A total of 21 pregnancies occurred during the Phase 3 trials; 13 in the minocycline foam, 4% group and eight in the vehicle group. Pregnancy outcomes in the minocycline foam, 4% group included seven healthy babies, 2 spontaneous abortions, 1 elective abortion, 1 ectopic pregnancy requiring laparoscopic salpingectomy, 1 baby with minor abnormalities (underweight, hyperbilirubinemia of prematurity, and hypoglycemia), and 1 pregnancy with outcome unknown (follow-up is continuing to determine pregnancy outcome). Jane Liedtka, MD, the reviewer from the Division of Pediatric and Maternal Health (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 (review dated July 15, 2019). We revised Section

8.1 (Pregnancy) to convey that the available data with use of minocycline foam, 4% are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

The currently available safety data from 3 Phase 3 trials with a treatment period of 12 weeks demonstrate that minocycline foam, 4% appears safe for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. The Applicant also submitted long-term safety data from an additional 40 weeks of treatment in 2 of the Phase 3 trials. The safety profile for long-term use (up to 52 weeks) of minocycline foam, 4% 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. Statistical Issues

The results for the co-primary efficacy endpoint of IGA success at Week 12 was variable across the three Phase 3 trials (FX2014-04, FX2014-05, and FX2017-22). Specifically, the response rates in Trial FX2017-22 in both treatment groups were much higher in comparison to the other two trials, see Table 14 in Section 8.1.4. A sensitivity analysis was conducted where centers with extreme results for IGA success were removed from the analysis to investigate their impact on the overall results. By removing the extreme centers, the IGA success rate decreased in both treatment groups; however, the treatment effect was similar to the overall population (i.e., 11.2% before removal and 10.0% after removal). The results for absolute change in inflammatory lesions also decreased in both treatment groups; however, the treatment effect remained the same. Refer to Section 8.1.6 for more details regarding the additional sensitivity analysis.

8.4. Conclusions and Recommendations

To establish the effectiveness of minocycline foam, 4%, the Applicant submitted data from three randomized, multicenter, double-blind, vehicle-controlled, Phase 3 trials (FX2014-04, FX2014-05, and FX2017-22). All 3 trials enrolled subject 9 years of age and older with moderate to severe acne vulgaris, defined as:

- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- IGA score of 3 (“moderate”) or 4 (“severe”)
- No more than 2 nodules on the face

In trials FX2014-04 and FX2014-05, subjects were randomized in a 2:1 ratio to treatment with minocycline foam, 4% or vehicle foam. In trial FX2017-22, the randomization was 1:1 to treatment with minocycline foam, 4% or vehicle foam. Subjects applied study drug to acne-affected areas (face, neck, back, etc.) once daily, up to a total of 4 grams per dose. The co-primary endpoints for all three trials were:

- Absolute change from baseline in inflammatory lesion counts at Week 12
- Proportion of subjects with IGA treatment success at Week 12, where success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from baseline at Week 12

Secondary endpoints included (b) (4) absolute change from baseline in inflammatory lesion counts and proportion of subjects with IGA treatment success at Week 9, and absolute change from baseline in inflammatory lesion counts and proportion of subjects with IGA treatment success at Week 6. For Trials FX2014-05 and FX2017-22, minocycline foam, 4% was statistically superior to vehicle for both co-primary efficacy endpoints (p-values ≤0.039). For Trial FX2014-04, minocycline foam, 4% was statistically superior to vehicle for absolute change in inflammatory lesion counts at Week 12 (p-value=0.008); however, minocycline foam, 4% was not statistically superior to vehicle for IGA success at Week 12 (p-value=0.181). Refer to Section 8.1.4 for discussion of the co-primary endpoints and Section 8.1.5 for discussion of the secondary endpoints.

The Applicant conducted a comprehensive assessment of safety of minocycline foam, 4% in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic TEARs.

Submitted safety and efficacy data support approval of NDA 212379, AMZEEQ™ (minocycline) topical foam for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients age 9 years 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.

10. Pediatrics

This product triggers Pediatric Research Equity Act considerations as a new formulation and has a PDUFA goal date of October 20, 2019. The Applicant submitted and followed the plan as identified in their Agreed iPSP.

In the Phase 3, Phase 2, and Phase 1 trials, the Applicant established the safety and efficacy of minocycline foam, 4% for use in the target pediatric population age 9 to less than 17 years for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. The Applicant requested a partial waiver of assessments in pediatric subjects from birth to less than 9 years of age because: "There is evidence that the drug or biological product would be ineffective or unsafe in that age group" (section 505B(a)(4)(B)(ii) of the Act). PeRC agreed with the Division that the assessments were adequate (August 7, 2019). Therefore, no

postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (21 CFR 314.55(b). Refer to Pediatrics and Assessment of Effects on Growth in Section 8.2.9 for a discussion regarding the Pediatric Study Plan.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton/container labels for minocycline foam, 4%. 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 reviewed the proposed PI, PPI and the carton and container labels for AMZEEQ (minocycline) topical foam, 4% and provided comments. The Division concluded that the PI and PPI were acceptable from a medication error perspective and that the container labels and carton labeling can be improved to increase the prominence of important information (e.g., established name, strength, storage conditions) and to facilitate product identification. (See review dated May 23, 2019). 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 August 21, 2019. These comments are reflected in final labeling. Table 35 provides the location of the labeling discussion for each section.

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 8.2.4, 8.2.5, 8.2.11
6 ADVERSE REACTIONS	Section 8.2.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Sections 5.5, 6.2, 6.3, 8.2, 10, 19.2
12 CLINICAL PHARMACOLOGY	Section 12.3. Pharmacokinetics (b) (4) Used arithmetic mean values instead of geometric mean values for PK parameters. Added standard deviation values of PK parameters. Moved descriptions of pediatric pharmacokinetics observed in FX2016-21 to the subsection 'Specific population - Pediatrics.'
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 Applicant submitted a proposed patient package insert (PPI) for minocycline foam, 4%. The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Susan Redwood, MPH, BSN, RN and Laurie Buonaccorsi, PharmD dated August 22, 2019.

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.

14. Division Director (DHOT) Comments

15. Division Director (OCP) Comments

16. Division Director (OB) Comments

17. Division Director (Clinical) Comments

I concur with the conclusions and recommendations of the review team. Please refer to the Executive Summary.

18. Office Director (or designated signatory authority) Comments

19. Appendices

19.1. References

The references are included as footnotes.

19.2. 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 FX2014-04, FX2014-05 and FX2017-22 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 FX2014-04

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study FX2014-05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 38		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study FX2017-22

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 90		

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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

19.3.1. Multiple of Human Exposure Calculations

The Applicant calculated ranges for the multiples of human exposure in the AMZEEQ label. The Applicant used 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 ng·hr/mL), the geometric mean AUC for adult subjects treated with AMZEEQ under maximal use conditions (20.7 ng·hr/mL), and the geometric mean AUC for pediatric subjects treated with AMZEEQ under maximal use conditions (46 ng·hr/mL).

The multiples of human exposure in the AMZEEQ 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 pediatric subjects treated with AMZEEQ under maximal use conditions (61.1 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)

The multiples of human exposure to be used in the AMZEEQ label are provided in Table 36. 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 AMZEEQ label.

Table 36: Multiples of Human Exposure Based on AUC Comparison Using the Human Mean AUC Value of 15475 ng*hr/mL Contained in the AMZEEQ Label

Study	Route	LOAEL[a]/NOAEL[b] (mg/kg/day)	Multiples of Human Exposure (SOLODYN)[c]	Multiples of Human Exposure (AMZEEQ)
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	759 (750)
Embryofetal development study in rats	Oral	10[a]	~1	253 (250)
Embryofetal development study in rabbits	Oral	100 [a]	~2	506 (500)
Pre- and postnatal development study in rats	Oral	50 [a]	~2.5	633 (650)

Study	Route	LOAEL[a]/NOAEL[b] (mg/kg/day)	Multiples of Human Exposure (SOLODYN)[c]	Multiples of Human Exposure (AMZEEQ)
Fertility and early embryonic development in rats	Oral	300[a]	~40	10120 (10000)
Fertility and early embryonic development in rats	Oral	100[a]	~15	3795 (3800)

[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.
Abbreviations: LOAEL = lowest-observed-adverse-effect level, NOAEL = no-observed-adverse-effect-level

19.3.2. 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 AMZEEQ label text.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

AMZEEQ is a tetracycline-class drug indicated to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. (1)

8.1 Pregnancy

Risk Summary

Available data with AMZEEQ 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. (b) (4) Systemic absorption of AMZEEQ in humans is (b) (4) low following topical administration of AMZEEQ (b) (4) *[see Clinical Pharmacology (12.3)]*. (b) (4) Because of (b) (4) low systemic exposure, it is not expected that maternal use of AMZEEQ 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 Precaution (5.1)* and *Use in Specific Populations (8.4)*].

(b) (4)

Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, ~~O~~oral administration (b) (4) of minocycline ~~administered~~ to pregnant rats and rabbits during the

period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ. (b) (4) [redacted] *see Data*]).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus [*see Warnings and Precautions (5.2)*].

(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, (b) (4) [redacted] 750 and 500 times (b) (4) [redacted] respectively, the systemic exposure at the MRHD (based on AUC comparison). (b) (4) [redacted]

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 (250 times the systemic exposure at the MRHD based on AUC comparison). (b) (4) [redacted]

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 (650 times the systemic exposure at the MRHD based on AUC comparison). (b) (4) [redacted] 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).

(b) (4)

12.1 Mechanism of Action

(b) (4)

The mechanism of action of AMZEEQ for the treatment of acne is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) 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.

(b) (4) 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.

(b) (4) Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (b) (4) 10,000 (b) (4) times the (b) (4) systemic exposure (b) (4) at the MRHD based on AUC comparison). (b) (4) However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (b) (4) 3,800 or 10,000 (b) (4) times (b) (4) the (b) (4) systemic exposure (b) (4) at the MRHD based on AUC comparison) (b) (4) 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.

(b) (4)

19.4. OCP Appendices (technical documents supporting OCP recommendations)

19.4.1. Individual Study Review

19.4.1.1. 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

Objectives

- To characterize minocycline pharmacokinetics following multiple-dose administration of FMX-101 minocycline foam, 4% in subjects with acne vulgaris
- To assess the relative bioavailability of FMX-101 minocycline foam, 4%, compared to Solodyn® (minocycline HCl) extended release tablets

Methods

This study was an open-label, 2-period, 2-treatment crossover evaluation of multiple-dose topical administration of minocycline foam, 4%, compared to oral administration of an approved listed product, Solodyn (minocycline HCl) extended release tablets. Thirty male and female patients with moderate to severe acne received following treatments with 10-day washout period:

- Period 1: a single dose of Solodyn extended release tablet, approximately 1 mg/kg with 240 mL water after an overnight fast of at least 10 hours. The dose of approximately 1 mg/kg was achieved by administering one of tablet strengths among 55 mg, 65 mg, 80 mg, 105 mg, and 114 mg based on body weight of each subject.
- Period 2: topical application of minocycline foam, 4%, approximately 4 g to the face, neck, upper chest, upper back, shoulder and upper arms, once daily for 21 days. The drug was applied in the study site by study personnel.

PK Assessment

Plasma samples for PK analysis were collected as following time points:

- Period 1: predose, at 30 minutes, 1, 1.5, 2, 3, 4, 6, 9, 12, and 16 hours after a single dose of Solodyn on Day 1, and on the morning of Day 2,3,4 and 5
- Period 2: predose and at 2, 4, 8, 12, 16, and 24 hours after first application (Day 1); predose on Days 6, 9, 10, 11, and 16; predose and at 2, 4, 8, 12, 16, and 24 hours after application on Day 12; predose and at 2, 4, 8, 12, 16, 24, 48, 72, and 96 hours after last application (Day 21)

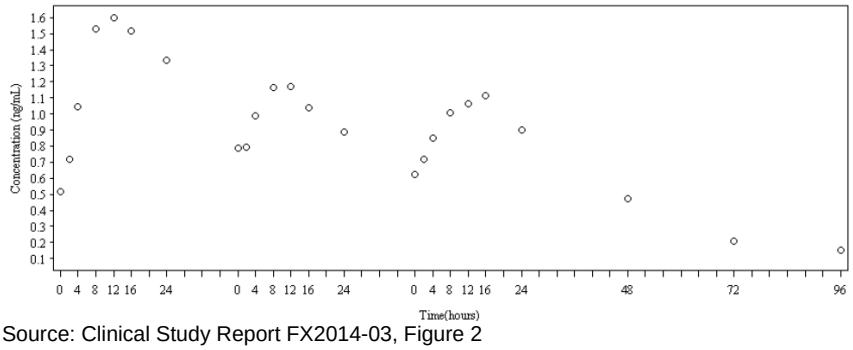
Plasma minocycline concentrations were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS) assays described in Section 19.4.2.

Result

A total 30 subjects were administered Solodyn approximately 1 mg/kg (range: 0.9 to 1.2 mg/kg) based on their body weight in Period 1 followed by minocycline foam, 4% approximately 4 g (range: 3.9 to 4.2 g).

Following topical administration of minocycline foam, 4%, plasma minocycline concentration increased until 8 to 14 hours (median T_{max} value) on Day 1, 12, and 21 (Figure 11). Accumulation over 21-day topical application was not apparent.

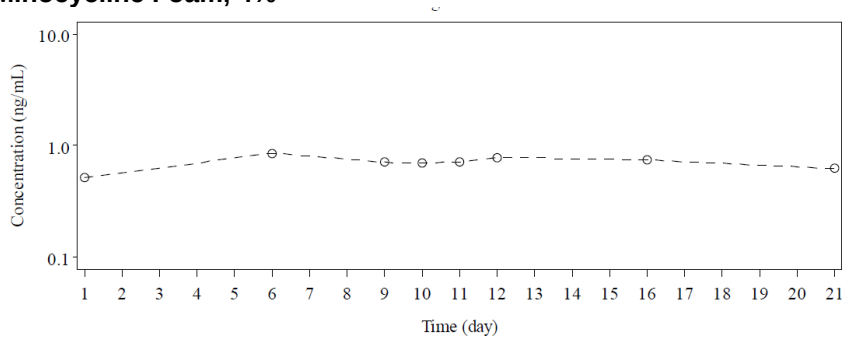
Figure 11: Mean Plasma Minocycline Concentration-Time Profile Following Daily Topical Application of Minocycline Foam, 4% 4 g Once Daily for 21 Days in Patients With Acne Vulgaris



Source: Clinical Study Report FX2014-03, Figure 2

The mean predose minocycline concentrations for Days 6 through 21 were not significantly different indicating that steady state was achieved by Day 6 (Figure 12).

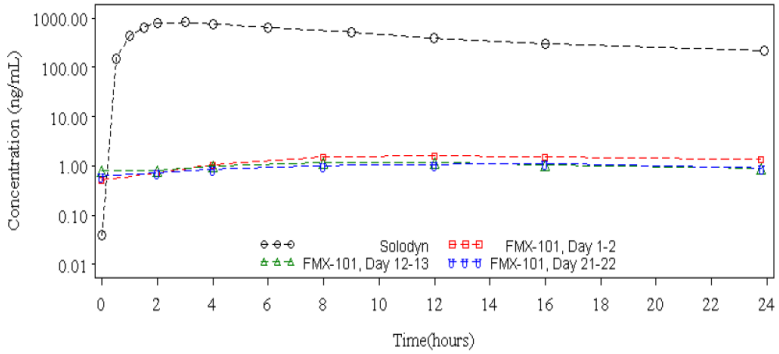
Figure 12: Mean Plasma Minocycline Predose Concentrations Over 21-Day Application of Minocycline Foam, 4%



Source: Source: Clinical Study Report FX2014-03, Figure 14.2.4.4.2

A comparison of the plasma minocycline concentration-time profiles over the first 24 hours after Solodyn or FMX-101, 4% administration is presented in Figure 13. Pharmacokinetic parameters are summarized in Table.

Figure 13: Mean Plasma Minocycline Concentration-Time Profiles Following Oral Administration of Solodyn and Topical Application of Minocycline Foam, 4% to Patients With Acne Vulgaris (Log-Linear Scale)



Source: Clinical Study Report FX2014-03, Figure 3

Table 37: PK Parameters Following Single Dose Oral Administration of Solodyn (~1 mg/kg Minocycline) and Topical Application of Minocycline Foam, 4% 4 g for 21 Days in Patients With Acne Vulgaris

PK Parameter	N	Mean (SD)	Median	Min, Max	CV (%)	Geometric Mean	Harmonic Mean
Period 1, Solodyn (~1 mg/kg minocycline)							
Day 1-5							
C_{max} (ng/mL)	30	873.367 (220.046)	801.00	603.00, 1620.00	25.20	850.049	--
T_{max} (h)	30	2.7 (0.81)	3.0	1.5, 4.0	30.01	--	--
AUC $_{0\text{-tldc}}$ (ng h/mL)	30	15227.30 (3624.298)	15363.00	9317.00, 25420.00	23.80	14823.41	--
kel (1/h)	30	0.044 (0.005)	0.04	0.03, 0.05	11.52	--	--
$AUC_{0\text{-inf}}$ (ng h/mL)	30	15474.57 (3690.744)	15553.50	9387.00, 25697.00	23.85	15060.29	--
$T_{1/2}$ (h)	30	16.0 (1.85)	15.9	12.8, 20.1	11.59	--	15.8
Period 2, FMX-101, 4% (4 g)							
Day 1-2							
C_{max} (ng/mL)	30	1.706 (0.823)	1.50	0.68, 3.88	48.26	1.539	--
T_{max} (h)	30	11.5 (4.01)	12.0	4.0, 23.8	35.00	--	--
C_{24} (ng/mL)	30	1.336 (0.667)	1.13	0.53, 3.09	49.91	1.192	--
$AUC_{0\text{-tau}}$ (ng h/mL)[1]	30	31.75 (14.950)	28.81	10.87, 72.56	47.09	28.70	--
Day 12-13							
C_{max} (ng/mL)	29	1.325 (0.787)	1.33	0.14, 3.27	59.40	1.063	--
T_{max} (h)	29	9.4 (5.13)	8.0	0.0, 23.8	54.33	--	--
C_{24} (ng/mL)	29	0.919 (0.531)	0.86	0.00, 2.01	57.76	0.869	--
$AUC_{0\text{-tau}}$ (ng h/mL)[1]	29	24.62 (14.100)	22.31	3.24, 55.69	57.26	20.06	--
Accumulation Ratio R [2]	29	0.85 (0.552)	0.76	0.00, 2.56	--	--	--
Day 21-25							
C_{max} (ng/mL)	30	1.253 (0.645)	1.02	0.41, 2.73	51.52	1.109	--
T_{max} (h)	30	12.3 (4.79)	14.0	4.0, 23.8	39.05	--	--
kel (1/h)	14	0.018 (0.006)	0.02	0.01, 0.03	32.59	--	--
$T_{1/2}$ (h)	14	44.3 (25.39)	37.8	26.7, 125.3	57.30	--	37.6
C_{24} (ng/mL)	30	0.901 (0.406)	0.77	0.30, 1.89	45.11	0.821	--
$AUC_{0\text{-tau}}$ (ng h/mL)[1]	30	23.02 (10.798)	20.45	6.28, 46.85	46.91	20.70	--
Accumulation Ratio R [2]	30	0.79 (0.368)	0.62	0.39, 1.66	--	--	--

SD = standard deviation. CV = coefficient of variation. Concentrations below the limit of quantitation (LOQ) were reported as zero for the purpose of calculating PK parameters.
1. $AUC_{0\text{-tau}}$ = AUC during the 24-hour dosing interval.
2. On Day 12, R = AUC $_{0\text{-tau}}$ Day 12 / AUC $_{0\text{-tau}}$ Day 1; On Day 21, R = AUC $_{0\text{-tau}}$ Day 21 / AUC $_{0\text{-tau}}$ Day 1.

Source: Clinical Study Report FX2014-03, Table 11-3

The ratio of minocycline C_{max} and AUC for FMX-101, 4% on Day 21 as compared to Solodyn was 0.131%, and 0.137% , respectively. Minocycline exposure following daily application of the approximately 4 g maximum use dose of FMX-101, 4% for up to 21 days was 730 to 794 times lower than that following a single oral dose of Solodyn (~1 mg/kg minocycline) (Table 38).

Table 38: Relative Bioavailability of Topical Application of Minocycline Foam, 4% 4 g for 21 Days Compared to Single Dose Oral Administration of Solodyn (~1 mg/kg minocycline)

		Geometric LSM Ratio (%)	
Parameters	**N**	**Estimate**	**90% CI**
C_{max}[1]	30	0.131	0.113, 0.151
AUC[2]	30	0.137	0.121, 0.156

Source: Clinical Study Report FX2014-03, Table 11-4
[1] C_{max} on Day 21 for minocycline foam compared to C_{max} on Day 1 for Solodyn
[2] $AUC_{0\text{-}24}$ on Day 21 for minocycline foam compared to $AUC_{0\text{-inf}}$ on Day 1 for Solodyn
Abbreviation: LSM = least square mean

Demographic characteristics in the PK population are summarized in Table 39. In the PK population, the mean age ranged from 18 to 30 years. A majority of subjects were White.

Table 39: Demographic Information of PK population in Study FX2014-03

	N=30
Age (yr)	
N	30
Mean (SD)	22.60 (3.23)
Median	22
Minimum, Maximum	18, 30
Gender N (%)	
Male	12 (40.0)
Female	18 (60.0)
Race N (%)	
White	27 (90.0)
Black or African American	3 (10.0)
Ethnicity N (%)	
Hispanic/Latino	11 (36.7)
Non-Hispanic/Latino	19 (63.3)

Source: Clinical Study Report FX2014-03, Table 11-2
Abbreviation: PK = pharmacokinetics

19.4.1.2. Study FX2016-21

Title: A Phase 1 study to characterize minocycline bioavailability in subjects with acne vulgaris following multiple dose topical administration of FMX101 in subjects 9 years to 16 years, 11 months of age

Objectives

- • To characterize minocycline PK after administration of FMX101, 4% once daily for 7 days under maximal use conditions in subjects 9 years to less than 17 years of age with acne vulgaris
- • To evaluate the safety and tolerability of FMX101, 4% administered once daily for 7 days under maximal use conditions in subjects 9 years to less than 17 years of age with acne vulgaris

Methods

This study was an open-label, parallel study following multiple dose topical administration of minocycline foam, 4%. Twenty subjects with moderate to severe acne were recruited in 3 age cohorts: 1) age 9 to 11 years, 2) age 12 to 14 years, and 3) age 15 years to less than 17 years of age. Subjects received the study drug approximately 4 g to the face, neck, upper chest, upper back, shoulder and upper arms, once daily for 7 days. The drug was applied in the study site by study personnel.

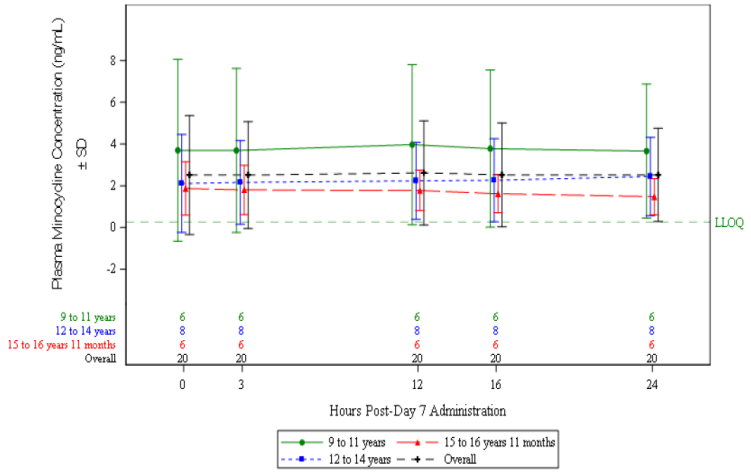
PK Assessment

Sparse plasma samples for PK analysis were collected at predose on Day 1 and at predose and 3 hours after dosing on Day 7, then on Day 8 at 12, 16, and 24 hours after the last application on Day 7. Plasma minocycline concentrations were determined using LC-MS/MS assays described in Section 19.4.2.

Result

Minocycline was quantifiable in all subjects on Day 7, after daily application of minocycline foam, 4% for 7 days. The levels of minocycline appear not to fluctuate much over the entire sampling interval on Day 7 (Figure 14). PK parameters of minocycline are presented in Table 40.

Figure 14: Plasma Concentrations of Minocycline Following Application of Minocyline Foam 4% 4 g Once Daily for 7 Days in Pediatric Patients With Acne Vulgaris



Source: Clinical Study Report FX2016-21, Figure 2
LLOQ = lower limit of quantitation, 0.257 ng/mL

Table 40: PK Parameters of Minocycline Following Application of Minocyline Foam, 4% 4 g Once Daily for 7 Days in Pediatric Patients With Acne Vulgaris

PK Parameter[1]	Statistic	Cohort and Age: Cohort 1 (9 to 11 years) (N=6)	Cohort 2 (12 to 14 years) (N=8)	Cohort 3 (15 to 16 years 11 months) (N=6)	Overall (N=20)
C_{max} (ng/mL)	Mean (SD)	4.45 (3.97)	2.78 (2.15)	2.04 (1.17)	3.06 (2.68)
	CV (%)	89.3	77.3	57.4	87.6
	Geometric Mean[2]	3.52	2.25	1.74	2.38
	Median	3.07	2.38	1.80	2.68
	Min, Max	1.56, 12.4	0.81, 7.72	0.62, 3.71	0.62, 12.4
T_{max} (h)	Mean (SD)	12.0 (10.7)	15.5 (10.6)	10.0 (11.8)	12.8 (10.7)
	CV (%)	89.4	68.1	118	83.3
	Median	12	20	6	12.1
	Min, Max	0, 24	0, 24	0, 24	0, 24
C_{24} (ng/mL)	Mean (SD)	3.66 (3.21)	2.45 (1.88)	1.48 (0.868)	2.52 (2.23)
	CV (%)	87.6	76.8	58.7	88.4
	Geometric Mean[2]	2.93	2.00	1.30	1.97
	Median	2.65	2.02	1.24	1.99
	Min, Max	1.40, 10.1	0.81, 6.75	0.62, 3.08	0.62, 10.1
$AUC_{0\text{-}tau}$ (ng*h/mL)	Mean (SD)	90.9 (90.2)	54.0 (46.2)	40.8 (23.8)	61.1 (59.2)
	CV (%)	99.2	85.6	58.3	96.9
	Geometric Mean[2]	68.2	42.2	35.1	46.1
	Median	61.4	41.2	35.5	44.7
	Min, Max	31.7, 271	13.5, 161	13.9, 79.4	13.5, 271

Source: Table 14.2.1 and Table 14.2.2

Abbreviations: $AUC_{0\text{-}tau}$ = area under the concentration-time curve from time zero (predose) through 24 hours; C_{24} = plasma minocycline concentration 24 hours after FMX101, 4% application; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; PK = pharmacokinetic; T_{max} = time to maximum measured plasma concentration

[1] Terminal phase rate constant (kel) and apparent terminal phase half-life ($T_{1/2}$) were not estimable because either there were fewer than 3 values in the terminal phase, the slope was positive, or the $T_{1/2}$ estimate was more than half the range of the terminal phase.

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

Source: Clinical Study Report FX2016-21, Table 9

Systemic exposure to minocycline in terms of AUC was 2.2-fold and 1.3-fold higher in the subjects aged 9 to 11 years and subjects aged 12 to 14 years compared to the subjects aged 15 years to <17 years of age.

Demographics characteristics in the PK population are summarized in Table 41. In the PK population, age of patients ranged from 10 to 16 years.

Table 41: Demographic Information of PK population in Study FX2016-21

	Cohort 1 (9 to 11 years) (N=6)	Cohort 2 (12 to 14 years) (N=8)	Cohort 3 (15 to 16 years 11 months) (N=6)	Overall (N=20)
Age (years)				
n	6	8	6	20
Mean (SD)	10.8 (0.41)	13.1 (0.64)	15.7 (0.52)	13.2 (1.99)
Median	11.0	13.0	16.0	13.0
Minimum, Maximum	10, 11	12, 14	15, 16	10, 16
Sex, n (%)				
Male	2 (33.3)	4 (50.0)	3 (50.0)	9 (45.0)
Female	4 (66.7)	4 (50.0)	3 (50.0)	11 (55.0)
Race, n (%)				
Black or African American	5 (83.3)	6 (75.0)	2 (33.3)	13 (65.0)
White	1 (16.7)	2 (25.0)	4 (66.7)	7 (35.0)
Ethnicity, n (%)				
Hispanic or Latino	0	0	2 (33.3)	2 (10.0)
Not Hispanic or Latino	6 (100)	8 (100)	4 (66.7)	18 (90.0)

Source: Clinical Study Report FX2016-21, Table 6
Abbreviation: PK = pharmacokinetics

Reviewer's comment:

- *Although the inclusion criteria indicated that the study was designed to include subjects aged 9 to <17 years of age, the youngest subject enrolled in this study was 10 years old. Therefore, in the labeling and the review, we referred the pediatric population studied to '10 to <17 years of age'.*
- *Within this pediatric PK study, younger pediatric patients tend to higher exposure than older pediatric patients. Likewise, Based on cross-study comparison with Study FX2014-03, the mean ± SD C_{max} and AUC_{0-24h} in overall pediatric patients were 2.4-fold and 2.7-fold higher than those observed in adult patients. This is probably because smaller and younger patients applied higher dose per body surface area than larger and older patients given the same amount of dose, 4 g/day, subsequently resulting in higher dermal absorption in younger patients.*

19.4.2. Summary of Bioanalytical Method Validation and Performance

Plasma minocycline concentrations were determined using chromatographic separation on a C8 column using gradient conditions with LC-MS/MS detection according to validated method (b) (4). Minocycline and the internal standard, minocycline-d6, were separated from human plasma by protein precipitation. A total of 1309 and 120 plasma samples were collected and analyzed from studies FX2014-03 and FX2016-21, respectively. The assay validation results are summarized in Table 42.

Table 42: Validation Results of the LC-MS/MS Bioanalytical Methods Used for Measuring Plasma Concentrations of Minocycline in FX2014-03 and FX2016-21

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)
ISR	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 pre-specified criteria (i.e., difference within ±20% of average of original and repeat value). FX2016-21: a total of 12 samples (10% of study samples) were re-analyzed and 11 samples (91.7%) were within the defined acceptance criteria.

Abbreviations: LC-MS/MS = liquid chromatography with tandem mass spectrometry; ISR = incurred sample reanalysis

19.5. Clinical/Biostatistics

Table 43: Results for the Percent Change in Inflammatory Lesion Counts at Week 12 [ITT[1]]

	Trial FX2014-04		Trial FX2014-05		Trial FX2017-22	
Endpoints	**AMZEEQ (N=307)**	**Vehicle (N=159)**	**AMZEEQ (N=312)**	**Vehicle (N=152)**	**AMZEEQ (N=738)**	**Vehicle (N=750)**
Percent change from baseline in inflammatory lesion counts						
Mean	-44%	-34%	-41%	-32%	-56%	-44%
LS mean[2]	-44%	-34%	-43%	-34%	-54%	-42%
Difference	-10%		-10%		-12%	
(95% CI)	(-17%, -3%)		(-17%, -2%)		(-16%, -8%)	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis except for Trial FX2014-05, which excluded Site 26 in the above table)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).

[2] Least square (LS) mean is based on analysis of covariance (ANCOVA) with treatment and investigational site as factors, and baseline value as a covariate.

Table 44: Results of the Co-Primary Efficacy Endpoints at Week 12 With Site 26 Included for Trial FX2014-05 [ITT[1]]

Endpoints	AMZEEQ (N=333)	Vehicle (N=162)
IGA success[2]	14.7%	7.9%
Difference (95% CI)	6.8% (0%, 12.7%)	
P-Vvalue[3]	0.042	
Absolute change from baseline in inflammatory lesion counts		
Mean	-13.5	-10.7
LS mean[4]	-13.8	-10.6
Difference (95% CI)	-3.2 (-5.4, -1.0)	
P-value[4]	0.005	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an Investigator's Global Assessment (IGA) score of 0 or 1 with at least a 2-grade reduction from baseline.
[3] P-value based on a Cochran-Mantel-Haenszel (CMH) test stratified by pooled investigational site.
[4] Least square (LS) mean and p-value based on analysis of covariance (ANCOVA) with treatment and pooled investigational site as factors, and baseline value as a covariate.

Table 45: Demographics of the Safety Population

Characteristic	Minocycline Foam, 4% n=1356	Vehicle Foam n=1058	Totals n=2414
Age group			
≥18 years	690 (50.9%)	544 (51.4%)	1234 (51.1%)
13–17 years	599 (44.2%)	458 (43.3%)	1057 (43.8%)
9–12 years	67 (4.9%)	56 (5.3%)	123 (5.1%)
Age			
Mean (SD)	20.19 [7.52]	20.41 [7.77]	20.29 [7.63]
Median	18	18	18
Range	9-66	9-59	9-66
Sex - count subjects and %			
F	807 (59.5%)	652 (61.6%)	1459 (60.4%)
M	549 (40.5%)	406 (38.4%)	955 (39.6%)
Race - count subjects and %			
White	1000 (73.7%)	780 (73.7%)	1780 (73.7%)
Black or African American	268 (19.8%)	206 (19.5%)	474 (19.6%)
Asian	54 (4.0%)	45 (4.3%)	99 (4.1%)
Multiple	30 (2.2%)	19 (1.8%)	49 (2.0%)
Native Hawaiian or other Pacific Islander	3 (0.2%)	5 (0.5%)	8 (0.3%)
American Indian or Alaska Native	1 (0.1%)	3 (0.3%)	4 (0.2%)
Ethnicity - count subjects and %			
Not Hispanic or Latino	890 (65.6%)	707 (66.8%)	1597 (66.2%)
Hispanic or Latino	466 (34.4%)	351 (33.2%)	817 (33.8%)

Source: Reviewer's table created in JReview using ISS dataset

Treatment-Emergent Adverse Reactions by Demographic Subgroup

The following tables display the treatment-emergent adverse reactions (TEARs) by age, sex, and race.

Table 46: Treatment-Emergent Adverse Reactions by Age Group

		Minocycline Foam, 4% n=1356			Vehicle Foam n=1058		
Body System or Organ Class	**Preferred Term**	**≥18 years**	**13 - 17 years**	**9 - 12 years**	**≥18 years**	**13 - 17 years**	**9 - 12 years**
Nervous system disorders	Headache	26 (1.9%)	12 (0.9%)	1 (0.1%)	14 (1.3%)	10 (0.9%)	1 (0.1%)

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

Table 47: Treatment-Emergent Adverse Reactions by Sex

		Minocycline Foam, 4% n=1356		Vehicle Foam n=1058	
Body System or Organ Class	**Preferred Term**	**Female**	**Male**	**Female**	**Male**
Nervous system disorders	Headache	27 (2.0%)	12 (0.9%)	20 (1.9%)	5 (0.5%)

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

Table 48: Treatment-Emergent Adverse Reactions by Race

		Minocycline Foam, 4% n=1356		Vehicle Foam n=1058	
Body System or Organ Class	**Preferred Term**	**Non-White**	**White**	**Non-White**	**White**
Nervous system disorders	Headache	21 (1.5%)	18 (1.3%)	8 (0.8%)	17 (1.6%)

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

Local Tolerability By Demographic Subgroups at Week 12

A total of 190 subjects in the Minocycline foam, 4% group and 181 subjects in the Vehicle group had missing local tolerability assessments at Week 12. Table 49, Table 50, and Table 51 below display local tolerability reactions by demographic subgroup.

Table 49: Local Tolerability at Week 12 by Age Group

	Minocycline Foam, 4% n=1166			Vehicle Foam n=877		
Parameter	**≥18 Years**	**13 - 17 Years**	**9 - 12 Years**	**≥18 Years**	**13 - 17 Years**	**9 - 12 Years**
Erythema	87 (7.5%)	83 (7.1%)	13 (1.1%)	75 (8.6%)	63 (7.2%)	8 (0.9%)
Hyperpigmentation	115 (9.9%)	60 (5.1%)	5 (0.4%)	83 (9.5%)	51 (5.8%)	8 (0.9%)
Dryness	47 (4.0%)	33 (2.8%)	4 (0.3%)	44 (5.0%)	41 (4.7%)	6 (0.7%)
Itching	44 (3.8%)	23 (2.0%)	2 (0.2%)	34 (3.9%)	24 (2.7%)	3 (0.3%)
Peeling	23 (2.0%)	14 (1.2%)	2 (0.2%)	24 (2.7%)	17 (1.9%)	2 (0.2%)

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

Table 50: Local Tolerability at Week 12 by Sex

	Minocycline Foam, 4% n=1166		Vehicle Foam n=877	
Parameter	**Female**	**Male**	**Female**	**Male**
Erythema	119 (10.2%)	64 (5.5%)	88 (10.0%)	58 (6.6%)
Hyperpigmentation	120 (10.3%)	60 (5.1%)	102 (11.6%)	40 (4.6%)
Dryness	56 (4.8%)	28 (2.4%)	63 (7.2%)	28 (3.2%)
Itching	41 (3.5%)	28 (2.4%)	35 (4.0%)	26 (3.0%)
Peeling	23 (2.0%)	16 (1.4%)	25 (2.9%)	18 (2.1%)

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

Table 51: Local Tolerability at Week 12 by Race

	Minocycline Foam, 4% n=1166		Vehicle Foam n=877	
Parameter	**Non-White**	**White**	**Non-White**	**White**
Erythema	35 (3.0%)	148 (12.7%)	23 (2.6%)	123 (14.0%)
Hyperpigmentation	86 (7.4%)	94 (8.1%)	69 (7.9%)	73 (8.3%)
Dryness	23 (2.0%)	61 (5.2%)	17 (1.9%)	74 (8.4%)
Itching	29 (2.5%)	40 (3.4%)	11 (1.3%)	50 (5.7%)
Peeling	10 (0.9%)	29 (2.5%)	9 (1.0%)	34 (3.9%)

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STROTHER D DIXON
10/17/2019 01:37:22 PM

HAMID R SHAFIEI
10/17/2019 06:29:14 PM

BARBARA A HILL
10/17/2019 06:34:40 PM

CHINMAY SHUKLA
10/18/2019 10:40:59 AM
Signing on behalf of Clinical Pharmacology Reviewer - Sojeong Yi, Ph.D. and myself as a Clinical Pharmacology Team Leader.

MATTHEW W GUERRA
10/18/2019 11:02:29 AM

MOHAMED A ALOSH
10/18/2019 11:40:34 AM

LAURA L JOHNSON
10/18/2019 11:49:14 AM

PATRICIA C BROWN
10/18/2019 11:52:47 AM

KEVIN L CLARK
10/18/2019 11:56:47 AM

Renqin DUAN
10/18/2019 11:58:01 AM

GORDANA DIGLISIC
10/18/2019 12:03:38 PM
Signing as the Clinical Team Leader and on behalf of Kendall A. Marcus, MD

Office of Antimicrobial Products (OND/CDER)
Division of Anti-Infective Products
Clinical Microbiology Review

Consult Review

NDA#: 212-379 (ORIGINAL) **Reviewer: Simone M. Shurland**

Date Company Submitted: 12/20/2018	**Date Received by CDER:** 12/20/2018	**Date Assigned:** 3/25/2019
Sponsor Name: Foamix Pharmaceuticals Inc	**Active Ingredient:** Minocycline hydrochloride	**Drug Category:** Anti-bacterial
Proposed Indications: Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older	**Dosage Form:** Foam	**Dose Administration:** Topical
	Dose Strength: 4%, 40 mg of micronized minocycline	**Dose Duration and Frequency:** Once daily application

DRUG PRODUCT NAME

Established Name:	AMZEEQ®
Active Ingredient:	Minocycline hydrochloride foam 4%
Non-Proprietary Name:	FMX101 4%,
Chemical Name:	
Molecular Weight:	Daltons
Molecular Formula:	(b) (4)
Structural Formula:	

TYPE OF APPLICATION: X Original NDA ☐ BLA ☐ NDA Supplement (sNDA) ☐ Annual Report
TYPE OF ASSESSMENT: ☐ 505(b)(1) X 505(b)(2) ☐ 351(a) ☐ 351(k)
REVIEW CLASSIFICATION: X Standard ☐ Priority ☐ Fast Track Designation
☐ Consult (Division) *Division of Dermatology and Dental Products (DDDP)* **☐ Other (please s*pecify*) ___**

CHEMICAL CLASSIFICATION

- ☐ **New Molecular Entity [NME] (Type 1)**
- ☐ **New Active Ingredient, Dosage form (Type 2)**
- ☐ **New Dosage Form (Type 3)**
- ☐ **New Combination (Type 4)**
- **X New Formulation or Manufacturer (Type 5)**
- ☐ **New Indication or Claim (Type 9)**

EFFICACY SUPPLEMENT CATEGORY:

- **X New Indication (SE1)**
- ☐ **New Dosing Regimen (SE2)**
- ☐ **New Route of Administration (SE3)**
- ☐ **Comparative Efficacy Claim (SE4)**
- ☐ **Labeling Change with Clinical Data (SE8)**
- ☐ **Animal Rule Confirmatory Study (SE10)**
- ☐ **Annual Report**
- ☐ **Period Benefit Risk Evaluation Safety Report in lieu of Annual Report**

SUMMARY

The Division of Dermatology and Dental Products (DDDP) requested the following consult:

The applicant has submitted NDA 212379 for minocycline foam, 4%. This is a 505(b)(2) NDA; the listed drug is Solodyn (minocycline HCl) Extended release tablets for oral use (NDA 50808). Clinical Microbiology previously provided consultative review for this product on 6/22/2017 under IND 122770. DDDP asked the sponsor in the EOP2 meeting (Feb 2, 2016) to propose plans to assess (b) (4) the protocols that are reviewed in the consult review from 6/22/2017. Please review

product labeling (Section 12.4 Microbiology) and advise whether the applicant has provided sufficient information to support their labeling claims regarding antimicrobial activity and microbial resistance. Please suggest edits to labeling as appropriate and attend applicable meetings.

FMX101 (minocycline hydrochloride 4%, AMZEEQ®) is proposed for topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years and older. The mechanism of action and activity of minocycline as an antibacterial drug is well known, (b) (4) This reviewer is unable to assess the effect of FMX101 treatment of non-nodular moderate to severe acne vulgaris (b) (4) it is recommended that no microbiology be provided in the labeling (more specifically in Section 12.4). This is consistent with recent NDA applications with similar indications and drug class. See Section 4 of this review (**FDA Review of the Labeling)** for the proposed labeling.

1. INTRODUCTION AND BACKGROUND

FMX101 (minocycline hydrochloride 4%, AMZEEQ®) is proposed for topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years and older. Minocycline is currently available as an oral drug under the brand names Dynacin®, Minocin ®, Solodyn® and Ximino®. It is also available in injectable products for intravenous administration. The Applicant proposed formulation consists of a micronized (b) (4) 4% minocycline hydrochloride filled into individual canisters (b) (4) Upon application of the foam onto the skin, the propellant evaporates and only the suspension remains in contact with the patient's skin.

2. PRE-CLINICAL MICROBIOLOGY

The activity of minocycline is well known. The following is a summary of the pre-clinical microbiology information conducted by the Applicant as well as based on published studies:

Minocycline belongs to the tetracycline class of antibiotics (b) (4)

Susceptibility testing of FMX101 were compared with minocycline powder (standard) against *Cutibacterium acnes* (formerly *Propionibacterium acnes*) using the agar or broth microdilution method in accordance with CLSI M11-A8 (2012) and M100-S27 (2017) guidelines (ILSE-P-012 [2018]). The FMX101 MICs against *C. acnes* isolates (n=8) ranged from 0.06 – 2 µg/mL by agar-dilution method. Notably, the FMX101 MICs were similar to minocycline powder against all *C. acnes* strains, suggesting that testing with either minocycline powder or FMX101 formulation provided equivalent results. The FMX101 MICs by the broth microdilution method were within ± one doubling dilution of the agar-based method. The vehicle used in the FMX101 formulation had no activity (> 32 µg/mL), suggesting that the vehicle does not contribute to the antimicrobial activity of FMX101.

Against phylogenetically and genotypical diverse set of 102 *C. acnes* clinical isolates primarily collected from the US, the FMX101 MIC_{90} values were 0.25 – 0.5 µg/mL, which were 4-fold more active than bacitracin and tetracycline, 8-fold more active than

clindamycin and 32-fold more active than benzoyl peroxide, neomycin, erythromycin, fusidic acid and mupirocin (IHMA-3114, FO02). The isolates tested also contained known tetracycline resistance mechanisms, variants in *rpsJ* encoding 30S ribosomal protein S10 with or without a mutation in 16S rRNA (G1058C mutation, *E. coli* numbering). This is similar to published literature which showed that the minocycline MIC_{90} values against *C. acnes* isolates ranged from 0.125 – 0.25 µg/mL (Hayashi 2011, Song 2011, Gonzalez 2010, Luk 2013, Mendoza 2013)

FMX101 and minocycline are bacteriostatic against *C. acnes* isolates after 48-hour exposure, having a minimal bactericidal concentration that is >32x MIC (ILSE-P-012 [2018], FO03).

The frequency of spontaneous mutations against 5 *C. acnes* strains showed that reduced susceptibility to FMX101 occurs at a low frequency ($<1 \times 10^{-8}$) at 2x or 4x MIC, no colonies were isolated on the 8x or 16x MIC concentration of minocycline (ILSE-P-013 [2018]). All isolates with reduced susceptibility had mutations leading to single amino acid changes in the 30S ribosomal subunit S10 (*rpsJ* gene) at positions 57 or 58. This gene and the altered amino acids have previously been reported in gram-positive and gram-negative species. The same amino acid variation was also identified based on genomic sequence data of several clinical isolates with lower intrinsic susceptibility to minocycline, further supporting *rpsJ* as the causal mutation in resistance. The FMX101 MICs in resistant mutants ranged from 2- to 16-fold greater than the parental strain; but were ≤ 0.5 µg/mL. One strain examined with an MIC of 0.25 µg/mL to minocycline possessed the RpsJ Y58D variant and failed to produce colonies with further reduced susceptibility, suggesting that secondary mutations may be rare ($<1 \times 10^{-9}$ in this study). Growth curve analysis of the mutant isolates revealed no apparent impact on fitness compared to parenteral strains. The MIC determination against comparator antibiotics indicated minimal cross-resistance to other antibiotics, including other members of the tetracycline-class. The inability to isolate mutants with minocycline MICs above 2 µg/mL and the identification of clinical isolates already containing this mutation with minocycline MIC at or below 2 µg/mL, suggest that the *rpsJ* mutations identify in the study may have limited impact to the overall minocycline susceptibility levels for *C. acnes.*

Several isolates of *C. acnes* with varied levels of intrinsic susceptibility to minocycline were assessed for emergence of resistance over the course of 15 serial passages (ILSE-P-014 [2018]). Cultures maintained anaerobically under minocycline-selective pressure for >30 days showed no increase in overall culture MIC (0/8 strains). No second-step mutations to previously isolated mutants or strains containing *rpsJ* mutations were isolated, including G1058C-equivalent *E. coli* 16S rRNA mutations. Thus, it appears 16S rRNA

mutations will occur at a much lower frequency than the isolation of *rpsJ* first-step mutations.

Based on dermal studies, the amount of minocycline in the upper and lower stratum corneum layers and viable skin were determined with the total intradermal minocycline concentrations being proportional to their respective minocycline concentrations in FMX101. The derived minocycline concentrations in the skin for total intradermal delivery were approximately 760 µg/mL for the 4% formulation and 168 µg/mL for the 1% formulation. For viable skin (i.e., below the stratum corneum) the values were 35.4 µg/mL and 14.0 µg/mL, respectively. Following 24 hours of exposure, the amount of minocycline was below the limit of quantitation (LOQ) in the receptor cells (LOQ = 2 µg/mL).

Reviewer's Comments:
The mechanism of action and in vitro activity of minocycline as an antibacterial drug is well known. (b) (4)
s consistent with other published studies.

3. CLINICAL STUDIES
The Applicant has completed two Phase 3 efficacy pivotal studies (Studies FX2014-05 and FX2017-22) and one Phase 3 efficacy supportive study (Study# FX2014-04).

Study FX2014-05 and FX2014-04 were similar in design which included two periods of a 12-week double-blind period during which study treatment (FMX101 or vehicle foam) was applied once daily, and a 40-week open-label extension period, during which all subjects received FMX101 on an as needed basis. Study FX2017-22 evaluated FMX101 compared to vehicle foam which was applied once daily for 12 weeks.

All studies assessed disease severity by inflammatory lesion counts, non-inflammatory lesions count and by an IGA score of facial acne on a 6-point scale where 0 = clear and 5 = very severe. The co-primary efficacy endpoints were the absolute change from baseline in inflammatory lesion count at Week 12 and treatment success (dichotomized as Yes/No) at Week 12, where success was defined as an IGA score of 0 or 1 (almost clear) and at least a 2-grade improvement (decrease) from baseline.

There were no clinical microbiology assessments (culture and sensitivity) and endpoints analyzed in any of the pivotal studies.

Reviewer's Comments:
This reviewer is unable to assess the effect of FMX101 treatment of non-nodular moderate to severe acne vulgaris (b) (4) *since, there were no clinical microbiology assessments* (b) (4) *in any of the pivotal studies.*

4. REVIEW OF LABELING

Reviewer's Comments:
(b) (4)
it is recommended that no microbiology be provided in the labeling. This is consistent with recent NDA applications with similar indications and drug class.

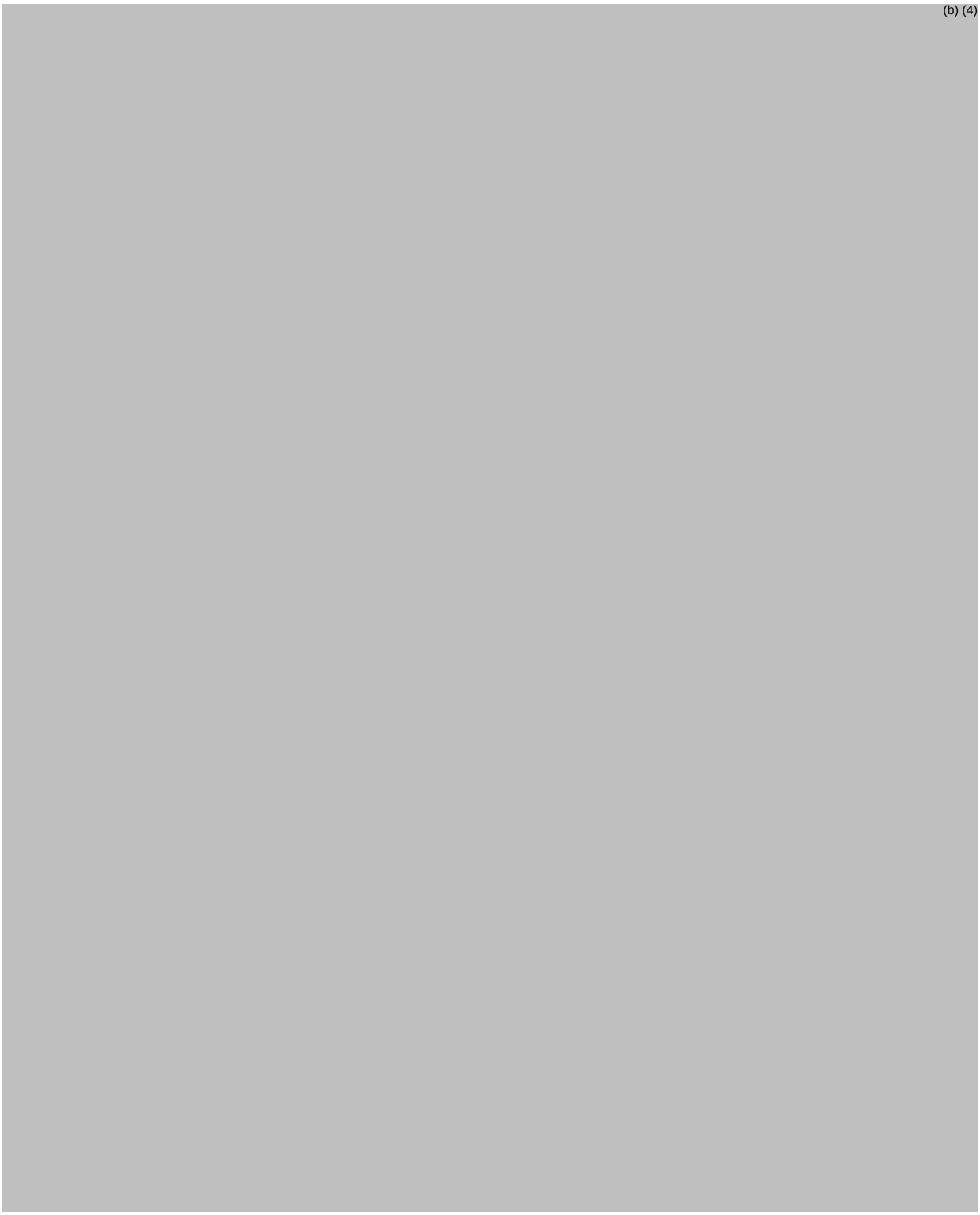
The Agency's proposed format of the microbiology subsection and related sections (12.1 and 12.4) should read as follows (Additions to the labeling are noted by double underline and deletions by strikethrough in red):

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

The mechanism of action of AMZEEQ for the treatment of acne is unknown

(b) (4)



Simone M. Shurland, PhD.
Clinical Microbiology Reviewer
DAIP HFD-520
July 26, 2019

Concurrence: Avery Goodwin PhD, Clinical Microbiology Team Leader

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SIMONE SHURLAND
07/26/2019 09:56:05 AM

AVERY C GOODWIN
07/26/2019 09:57:34 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	122770
Supporting document/s:	SDN # 36
Sponsor's letter date:	10-12-2017
CDER stamp date:	10-12-2017
Product:	FMX-101 (Minocycline Hydrochloride Foam) 4%
Indication:	Treatment of (b) (4) inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients (b) (4) years of age and older
Sponsor:	Foamix Pharmaceuticals Inc
Review Division:	Dermatology and Dental Products
Reviewer:	Renqin Duan, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
Project Manager:	Barbara J Gould

Template Version: September 1, 2010

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Minocycline (hydrochloride) is a semi-synthetic derivative of tetracycline. Its oral dosage form is prescribed for the treatment of acne. Minocycline hydrochloride is available in several oral formulations under the brand names Dynacin®, Minocin®, Myrac®, and Solodyn®. Solodyn® (Minocycline Hydrochloride) Extended-Release Tablets was approved by the FDA in 2006 for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

The sponsor is developing its drug product, FMX-101 (minocycline hydrochloride foam) 4%, for topical treatment of (b) (4) inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients (b) (4) years of age and older. The initial IND was submitted on February 13, 2015. An End-of-Phase 2 meeting was conducted on February 17, 2016.

The sponsor requests a waiver for conduct of a dermal carcinogenicity study with its product, FMX-101 under this submission.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor intends to rely on the Agency's previous findings of safety for the listed drug (Solodyn® [Minocycline Hydrochloride] Extended-Release Tablets) to support the submission of a 505(b)(2) New Drug Application (NDA) for FMX-101 minocycline hydrochloride foam.

According to the Solodyn label, minocycline was not mutagenic in a battery of in vitro and in vivo genetic toxicity studies.

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.

The sponsor submitted a 39-week dermal toxicity minipig study to support its request for a waiver for the conduct of a dermal carcinogenicity study with its product, FMX-101 under this submission.

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). 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 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 signs of illness or adverse reaction including at the dose sites. The NOAEL for both local and systemic toxicity 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) based on the results from this study. The C_{max} and AUC_{last} values associated with this NOAEL were 82.5 ng/mL and 1160 hr*ng/mL.

Therefore, a waiver request for conduct of a dermal carcinogenicity study with FMX-101 is granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: N/A

No clinical study protocol was included in this submission. The sponsor submitted a waiver request for the conduct of a dermal carcinogenicity study with its product, FMX-101 under this submission. This reviewer recommends that the sponsor's request for a waiver for conduct of a dermal carcinogenicity study with FMX-101 be granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs.

1.3.2 If Not Safe to Proceed

Nonclinical deficiencies: N/A

Nonclinical information needed to resolve deficiencies: N/A

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

It is recommended that the following comments be relayed to the sponsor for IND 122770.

Your waiver request for conduct of a dermal carcinogenicity study with FMX-101 (minocycline hydrochloride foam, 4%) is granted based on the results from your 39-week dermal toxicity study with minocycline foam in minipigs.

2 Drug Information

2.1 Drug

CAS Registry Number: 13614-98-7

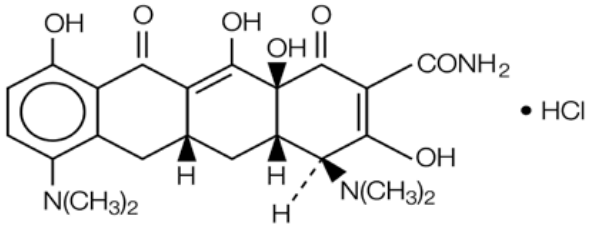
Generic Name: minocycline hydrochloride foam, 4%

Code Name: FMX-101

Chemical Name: [4S(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12atetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride

Molecular Formula/Molecular Weight: $C_{23}H_{27}N_3O_7$•HCl/493.95

Structure:



Pharmacologic Class: Tetracycline

2.2 Relevant INDs, NDAs, BLAs and DMFs

This IND makes reference to DMF (b) (4) and NDA 50808 (Solodyn® [Minocycline Hydrochloride] Extended-Release Tablets), approved on May 8, 2006, as the listed drug.

2.3 Drug Formulation

The FMX-101(minocycline hydrochloride foam, 4%) drug product (b) (4) minocycline hydrochloride (equivalent to 4% minocycline) developed as a foam product for topical treatment of acne. The quantitative composition of FMX-101 is provided in the following table.

Table 1 Composition of FMX-101 4% Foam

Component	CAS Number	Quantitative Composition (% w/w)	Quantity Per 35 g Container (g)
Bulk			
Minocycline Hydrochloride (expressed as minocycline)	13614987	4.00[a]	1.40[a]
Soybean Oil		(b) (4)	
Coconut Oil			
Light Mineral Oil			
Cyclomethicone			
Cetostearyl Alcohol			
Stearic Acid			
Myristyl Alcohol			
Hydrogenated Castor Oil			
White Wax (Beeswax)			
Stearyl Alcohol			
Docosanol			
Total Bulk			
(b) (4) (butane + isobutane + (b) (4) propane)	Butane		
	Isobutane		
	Propane		
			(b) (4)

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

N/A

2.6 Proposed Clinical Protocol

No clinical protocol was included in this submission.

2.7 Previous Clinical Experience

The clinical safety profile of oral minocycline in subjects with acne vulgaris has been well established. Adverse reactions (incidence ≥5%) that have been reported with Solodyn include headache, fatigue, dizziness, and pruritus.

Systemic absorption of minocycline may cause hyperpigmentation, central nervous system effects (light-headedness, dizziness, or vertigo), pseudotumor cerebri (benign intracranial hypertension), autoimmune syndromes, liver injury, photosensitivity, bacterial resistance, and has been associated with clostridium difficile associated diarrhea (CDAD), anaphylaxis, serious skin reactions, erythema multiforme, and

DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. In addition, like other tetracycline-class drugs, minocycline can cause fetal harm when administered to a pregnant woman and may cause permanent discoloration of teeth during tooth development.

To date, the sponsor has completed two clinical trials in Israel with minocycline foam (up to 4%) for up to 12 weeks: a pilot Phase 1 PK trial in healthy subjects with or without acne (Trial FMX101-1) and a Phase 2 dose-range finding trial of minocycline foam in subjects with acne vulgaris (Trial FX2010-03).

The sponsor has conducted two maximal use studies to evaluate the safety and tolerability of FMX101 and to characterize minocycline pharmacokinetics (PK) in adults and pediatrics. The PK data from those studies will be used to establish a clinical bridge to Solodyn® (minocycline HCl) Extended Release Tablets, the reference listed drug for this 505(b)(2) development program.

2.8 Regulatory Background

A Pre-IND teleconference was conducted between the Agency and the sponsor on July 30, 2014. The meeting minutes containing the following Pharmacology/Toxicology comments were relayed to the sponsor on August 13, 2014.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

The initial IND was submitted on February 13, 2015 with a Phase 1 study to characterize minocycline bioavailability following multiple dose topical administration of FMX-101 compared to oral administration of Solodyn.

An End-of-Phase 2 meeting was conducted between the Agency and the sponsor on February 17, 2016. The meeting minutes containing the following Pharmacology/ Toxicology comments were relayed to the sponsor on March 8, 2016.

Pharmacology/Toxicology

Foamix's Position

Since minocycline has not been approved by the dermal route, Foamix's nonclinical development plan included evaluation of the toxicity and toxicokinetics of minocycline HCl foam in repeat-dose dermal toxicity studies in minipigs. Foamix considers data from the 3-week minipig study (S12919) and the 12-week minipig study (S12917), in addition to the human safety data generated in Phase 2 clinical acne vulgaris study FX2010-03, adequate to support the planned Phase 3 trial in acne vulgaris that will employ once daily treatment for 12 weeks. The reports for the 3-week and 12-week minipig studies have been submitted to the IND and are summarized in Section 10.2.1.

Question 3:
Does the Division concur that the completed 12-week dermal toxicity study in minipigs is adequate to support the 12-week Phase 3 trial?

Response:
Yes, we agree.

Foamix's Position

A 39-week dermal toxicity study of FMX-101 foam in Hanford minipigs with a 4-week recovery period is scheduled to initiate on February 9, 2016. This study is intended to support the NDA as well as a long-term-extension portion of the Phase 3 studies in which patients will be dosed for more than 12 weeks. Per agreement with the Division at the pre-IND meeting held on July 30, 2014, we plan to support enrollment of patients in the 9-month extension with the 12-week dermal minipig study and the ongoing 39-week dermal minipig study in which animals will be treated with FMX-101 for at least one month more than the human subjects at any point in time.

Study protocol for "A 39-Week Dermal Toxicity Study of FMX-101 Foam with 4-week Recovery in Hanford Minipigs" can be found in **Appendix C** along with protocol outlines for the planned guinea pig dermal sensitization study and bovine corneal opacity and permeability study.

Question 4:
Does the Division agree with the design of the 39-week (ongoing) and planned nonclinical toxicity studies?

Response:
Overall, the design of the ongoing 39-week dermal toxicity study in minipigs and the planned nonclinical toxicity studies including guinea pig dermal sensitization and bovine corneal opacity and permeability studies appear acceptable. The adequacy of these studies will be determined after review of the final study reports.

(b) (4)

Question 5:
Does the Division concur that the nonclinical toxicity studies completed to date, ongoing, (b) (4) (b) (4) will be adequate to support the NDA filing?

(b) (4)

3 Studies Submitted

3.1 Studies Reviewed

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

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No pharmacology studies were conducted with Minocycline HCl foam. The following statement is included in the Solodyn label.

12.1 Mechanism of Action

The mechanism of action of SOLODYN for the treatment of acne is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of SOLODYN for the treatment of acne are unknown.

The following summary is from the sponsor's submission.

Minocycline is a semi-synthetic derivative of tetracycline. It inhibits growth of bacteria and is anti-inflammatory. (b) (4) The lipophilicity of

minocycline is greater than other tetracyclines, indicating it may partition to a greater extent into sebum than other tetracyclines do.

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

No standalone safety pharmacology studies were conducted with Minocycline HCl foam.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The following information is included in the Solodyn label.

12.3 Pharmacokinetics

SOLODYN Tablets are not bioequivalent to non-modified release minocycline products. Based on pharmacokinetic studies in healthy adults, SOLODYN Tablets produce a delayed Tmax at 3.5-4.0 hours as compared to a non-modified release reference minocycline product (T_{max} at 2.25-3 hours). At steady-state (Day 6), the mean $AUC_{(0–24)}$ and C_{max} were 33.32 µg×hr/mL and 2.63 µg/mL for SOLODYN Tablets and 46.35 µg×hr/mL and 2.92 µg/mL for Minocin® capsules, respectively. These parameters are based on dose adjusted to 135 mg per day for both products.

A single-dose, four-way crossover study demonstrated that SOLODYN Tablets used in the study (45 mg, 90 mg, 135 mg) exhibited dose-proportional pharmacokinetics. In another single-dose, five-way crossover pharmacokinetic study, SOLODYN Tablets 55 mg, 80 mg, and 105 mg were shown to be dose-proportional to SOLODYN Tablets 90 mg and 135 mg.

When SOLODYN Tablets were administered concomitantly with a meal that included dairy products, the extent and timing of absorption of minocycline did not differ from that of administration under fasting conditions.

Minocycline is lipid soluble and distributes into the skin and sebum.

The pharmacokinetics of minocycline associated with dermal administration of Minocycline HCl foam was conducted in Hanford minipigs in parallel with the repeat-dose toxicology evaluations (see Section 6.2).

Methods of Analysis

The analysis of minocycline in Hanford minipig plasma with K_2EDTA was conducted utilizing a validated LC-MS/MS method. The calibration range was 0.500 to 250 ng/mL,

and the regression type was linear $1/x^2$ concentration weighting. (b) (4) was the internal standard. The sponsor submitted an interim report (pending long term frozen stability evaluation) for the following study.

Full Validation of an LC-MS/MS Assay for Minocycline in Hanford Minipig plasma with K_2EDTA (Study # 2314-001)

Based on the results from this study, an LC-MS/MS method for the determination of Minocycline concentrations in Hanford minipig plasma with K_2EDTA has been successfully validated. The calibration range of the method is 0.500 to 250 ng/mL for Minocycline using a 50 µL sample aliquot. The results indicate the method is sensitive, selective, accurate, and reproducible. Minocycline is stable during storage, processing, and analysis.

5.2 Toxicokinetics

Included in toxicity study.

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

Study title: A 39-Week Dermal Toxicity Study of FMX-101 Foam With 4-Week Recovery in Hanford Minipigs

Study no.:	S13145
Study report location:	Electronic submission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	01-11-2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	FMX-101 4% (Minocycline hydrochloride foam 4%), batch # 5111801, 6031601 FMX-101 8% (Minocycline hydrochloride foam 8%), batch # 5111601, 6031001 FMX-101 16% (Minocycline hydrochloride foam 16%), batch # 5102201, 6031401, 6072501

Key Study Findings

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). 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 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 signs of illness or adverse reaction including at the dose sites. The NOAEL for both local and systemic toxicity 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) based on the results from this study. The C_{max} and AUC_{last} values associated with this NOAEL were 82.5 ng/mL and 1160 hr*ng/mL.

Methods

Doses:	0 (untreated control), 0 (vehicle control), 4%, 8% and 16%, corresponding to 0, 0, 10, 20 and 40 mg/kg/day minocycline
Frequency of dosing:	Once daily
Route of administration:	Topical
Dose volume:	0.25 g/kg/day
Formulation/Vehicle:	Foam/Clinical formulation
Species/Strain:	Sus scrofa/Hanford minipig
Number/Sex/Group:	4
Age:	5 months at Day 1
Weight:	14.4 to 22.7 kg
Satellite groups:	2/sex/group for recovery for Groups 2 and 5
Unique study design:	N/A
Deviation from study protocol:	There were no major deviations from the protocol which significantly affect the integrity or outcome of the study.

Observations and Results

Mortality

Observation for mortality/moribundity was conducted twice daily (AM and PM).

There was no moribundity or mortality during the study.

Clinical Signs

Physical examination was performed during acclimation, and weekly after dose initiation. Detailed clinical observations were performed once daily during acclimation through termination.

Dose site observations were performed daily in the first week prior to and post dose; once weekly after the first week of dosing and during recovery. A modified Draize Scoring System was used to determine the degree of inflammation (erythema and edema).

Most clinical findings were those commonly seen in laboratory swine (abrasions, scabs, ocular discharge, hoof cracks, etc.), and were not considered test article related.

There were no clinical dose site findings for the first three weeks after dose initiation for all groups. From the fourth week on, sporadic skin reactions (slight erythema, rash, papule etc.) were observed across all treated groups (groups 2-5) with a low magnitude. Overall, the most common dose site findings from week 4 through the end of the study included patchy erythema, scabbing, discoloration (staining), rash and small papules. The findings were more common and remarkable in the vehicle control animals (Group 2). The dose site findings in the test article treated groups (low, mid and high) were considered incidental with remarkably lower frequencies and severities compared to those in the vehicle control group throughout the entire study period. The findings, when they occurred, were transient and without a dose-response relationship. The dose site findings were therefore not considered to be test article-related.

Draize scores showed that there were no scores above a 1 assessed for Group 1 (untreated) males and females at any time during the study, and the majority of scores assessed for all study animals were either 0 or 1 for the first six weeks of treatment. From Weeks 7 to 40, there were infrequent erythema and edema scores of 2, most of which occurred in vehicle-treated animals, most notably during Weeks 31 to 34 due to rashes and/or papules developed on the dose sites.

There was only one instance during this study that an animal was given an erythema score >2 (animal 5F2 was given a score of 3 in Week 34 but was normal by Week 36 through termination). However, the majority of erythema and edema scores for all other treatment groups were either 0 or 1.

Body Weights

Animals were weighed once during acclimation, weekly thereafter, and prior to termination. Body weight change from the previous measurement was calculated for each animal.

No test article related effects on body weight were noted during the study.

Feed Consumption

Qualitative food consumption was determined daily with exceptions of a few days.
No test article related effects on food consumption were noted during the study.

Ophthalmoscopy

Ophthalmology examinations were performed on all animals during acclimation on Day -6 and Week 39 (Day 269).

There were no test article related ophthalmic findings during the study.

Because there were no significant ocular findings on Day 269 for recovery animals, no ophthalmology examinations were performed at the end of recovery phase.

ECG

Electrocardiographs (ECG) were obtained from all animals during acclimation (Day -7), and Week 39 (Day 267). The appropriate electrodes were attached. Recordings of the standard leads I, II, and III (at a minimum) were collected. The ECG raw data was recorded on appropriate ECG paper. The data was sent to a board certified veterinary cardiologist ((b) (4)) who analyzed the recordings for each animal. Each ECG trace was qualitatively examined for abnormalities in rhythm and conduction, and routine ECG measurements were obtained for HR, RR, PR, QRS, QT, and QTc.

There were no test article-related changes in electrocardiography parameters and all the electrocardiograms evaluated in this study were qualitatively and quantitatively considered normal for the minipigs.

The mean heart rate appeared lower (mean RR interval increased) compared to those from the two control groups for both males and females in Week 39 at all three dose levels. The mean heart rate was also lower (mean RR interval increased) for the high dose Group 5 animals compared to the Control Group 2 for both males and females at the end of the recovery period. The heart rate changes also took place in the control groups but were not as pronounced. Since there were no other changes and all measured heart rates were within the normal range and were similar for all groups and there were no dose responses, the heart rate differences between the test and control groups were considered insignificant, not test article-related and to be physiological variations.

Hematology

Hematology and coagulation evaluation were conducted during acclimation (Day -11), Day 268 on all animals (main and recovery) at the main animal termination time point, and on recovery animals prior to termination (Day 302). Animals were fasted the day before blood collection. Blood samples were obtained from all animals via jugular vein or other appropriate vessel.

K_3EDTA was used as anticoagulant for hematology analysis. Sodium citrate (3.2%) was used as the anticoagulant for coagulation evaluation. Plasma was prepared by centrifuging for approximately 15 minutes at 3000 rpm at 4°C.

At the main cohort termination time point, statistically significant decreases in absolute and relative basophil counts for high dose male animals relative to Group 2 controls were observed (see the following table).

Gender		Males					Females				
Group		1	2	3	4	5	1	2	3	4	5
Treatment (mg/kg/day)		Sham	0	10	20	40	Sham	0	10	20	40
N		4	6	4	4	6	4	6	4	4	6
Basophils	$\times 10^3/\mu L$	0.15	0.14	0.09	0.07	0.06[a]	0.10	0.10	0.09	0.11	0.07
	%	1.1	1.1	0.8	0.6	0.5[a]	0.9	0.8	0.8	1.1	0.6

There were no other test article related hematology and coagulation changes in this study.

Clinical Chemistry

Clinical chemistry analysis was conducted during acclimation (Day -11), Day 268 on all animals (main and recovery) at the main animal termination time point, and on recovery animals prior to termination (Day 302). Animals were fasted the day before blood collection. Blood samples (3 mL/animal) were obtained from all animals via jugular vein or other appropriate vessel. Sodium citrate (3.2%) was used as the anticoagulant. Serum samples were prepared by centrifuging blood samples at 3000 rpm for ~ 15 minutes at 4°C.

There were no test article related effects on any clinical chemistry parameters in this study.

Urinalysis

Urinalysis were conducted during acclimation (Day -11), Day 268 on all animals (main and recovery) at the main animal termination time point, and on recovery animals prior to termination (Day 302). Animals were fasted the day before blood collection. Blood samples were obtained from all animals via jugular vein or other appropriate vessel. Urine samples (at least 1 mL/animal) were collected from metabolism cages at room temperature.

There were no statistically or clinically significant test article related effects on any urinalysis parameters in this study.

Gross Pathology

At scheduled termination, animals were sedated with IM administration of Telazol (2.2 mg/kg) plus Xylazine (0.44 mg/kg) then euthanized with IV administration of Fatal Plus (minimum 1 mL/4.5 kg body weight). A scheduled terminal necropsy was performed on each animal under the direct supervision of a board-certified veterinary pathologist. All necropsies included examination of the external skin, all orifices, and the cranial, thoracic, abdominal and pelvic cavities.

There were several findings noted in one untreated control animal (1M1), several vehicle-treated (Group 2) animals, and one high dose treated animal (5F5) during the Main Termination necropsy (see the following table).

Table 23 Individual Necropsy Findings and Histopathology Correlations

Study ID	Animal ID	Findings	Histopathology Correlations
1M1	9835	Stomach: Multifocal 2-3 cm long linear erosion/ulcer; glandular stomach	Within Normal Limits
2M2	9827	Dose site skin multiple 2-3 cm linear wavy dark brown to black scabs	Mild chronic/active, ulcerative inflammation
2M3	9841	Dose site skin multiple 2-3 cm linear wavy dark brown to black scabs	Not considered a lesion by the necropsy pathologist. Dose site skin appeared normal in histopathology
2F2	9830	Multiple 2-3 cm linear to circular black dark brown scabs (dose area)	Mild chronic/active, ulcerative inflammation
2F6	9848	Skin is very firm over the treatment area	Not considered a lesion by the necropsy pathologist. Not analyzed (recovery animals).
5F1	9849	Left adrenal failed to harvest	
5F5	9829	2.5 x 3.5 cm firm mass located just behind the poll in the subcutis. On section, mass contains caseous material	Sample was reserved, but finding was not considered test article-related. The finding was considered related to vaccine injection

The findings from the sham control animal (1M1: stomach erosion/ulcer) and the high dose animal 5F5 (neck mass contained caseous material – related to vaccination) were apparently not related to any treatments. The observations of multiple 2-3 cm linear wavy dark brown to black scabs or linear to circular black dark brown scabs for some of the vehicle control group animals (2M2, 2M3 and 2F6) were most likely related to treatment with the vehicle. The findings were clearly developed (healing) from the skin rash observed (slight to moderate) during the treatment phase of the study. Therefore, all necropsy findings noted in the Main and Recovery animals were considered either incidental or unrelated to treatment with the test article.

Organ Weights

At scheduled euthanasia, the following organs were weighed. Paired organs were weighed together. Organ-to-body weight and organ-to-brain weight ratios were calculated.

adrenal (2)	kidney (2)	prostate
brain (cerebellum, cerebrum, medulla & pons)	liver with gall bladder (drained)	spleen
epididymis	ovary (2)/testis (2)	thymus
heart	pituitary	thyroid/parathyroid (2)
		uterus

At Main Termination, thymus weight relative to brain weight in high dose females showed a statistically significant increase compared to Group 2 vehicle control animals.

Gender		Males					Females				
Group		1	2	3	4	5	1	2	3	4	5
Treatment (mg/kg/day)		Sham	0	10	20	40	Sham	0	10	20	40
N		4	4	4	4	4	4	4	4	4	4
Absolute Weight (g)	Mean	14.501	17.333	17.194	12.740	14.631	21.022	14.136	19.811	18.168	28.108
	SD	7.886	5.923	6.701	1.368	5.251	8.845	2.017	6.987	7.042	3.413
Per BW (%)	Mean	0.0266	0.0322	0.0302	0.0231	0.0287	0.0453	0.0301	0.0381	0.0388	0.0510
	SD	0.0130	0.0129	0.0097	0.0020	0.0089	0.0112	0.0027	0.0103	0.0122	0.0052
Per Brain Weight (%)	Mean	14.6	16.6	17.0	12.3	14.7	21.5	14.7	20.1	17.6	**29.3***
	SD	8.0	5.3	6.0	1.4	3.7	8.5	2.5	7.6	6.8	3.3

There were no other significant changes on organ weights.

Histopathology

Adequate Battery: Yes

The following tissues from all animals were preserved in 10% neutral-buffered formalin except as noted. All collected tissues including administration site skin samples from all animals were submitted to [redacted] (b) (4) for standard histopathology analysis.

adrenal (2)	ovary (2)
aorta	pancreas
bone (femur & sternum with marrow)	pituitary gland
bone marrow smear (BMS)*	prostate
brain (cerebellum, cerebrum, medulla & pons)	rectum
cecum	salivary gland [mandibular (2)]
cervix	sciatic nerve
colon	seminal vesicle (2)
duodenum	skeletal muscle (quadriceps femoris)
epididymis (2)	skin (abdominal region – non-dose site)
esophagus	skin (dorsal/shoulder region – non-dose site)
eyes with optic nerve (2)**	skin (dose application site)
heart	spinal cord (cervical, thoracic & lumbar)
ileum	spleen
jejunum	stomach (cardiac, fundic, pyloric, and esophageal glands)
kidney (2)	testis (2)**
lacrimal gland	thymus
lesions***	thyroid/parathyroid (2)
liver with gall bladder	tongue
lung (with main stem bronchi)	trachea
lymph node (mandibular)	urinary bladder
lymph node (mesenteric)	uterus
mammary gland (females)	vagina

* BMS, fixed with methanol; ** Fixed in Davidson's (eyes) or modified Davidson's solution (testes) for 1 day and stored in 70% alcohol; *** Gross lesions were collected at the discretion of the Pathologist.

Peer Review: Yes

Tissues as described below were included for the peer review.

- All tissues from 2 animals/sex (randomly selected) from vehicle control and high dose groups in the main study phase.
- All skin sections from all Main study animals.

Histological Findings

Under the conditions of this study, there were no macroscopic or microscopic findings in Hanford minipigs related to the administration of minocycline hydrochloride foam at concentrations up to 16% for 39 weeks. There were no signs of dermal or systemic toxicity related to the test article and no proliferative changes were observed in the skin. No preneoplastic, hyperplastic or other histological changes were reported in the skin or any other tissue of the animals. Some mild changes observed in the dose application site of a few Group 2 animals may have been associated with the vehicle.

Pathology peer review showed that there were no additional pathology findings.

Special Evaluation

N/A

Toxicokinetics

At least 2 mL of blood samples for TK analysis were collected into tubes containing K2EDTA anticoagulant from all animals via the jugular or other appropriate vessel at the time-points defined in the following table.

TK Series	Animals	Time Points
Week 4, 20, 39	All animals in Group 1 and 2	1 hour post-dose
	All animals in Group 3, 4 and 5	Time 0 (pre-dose), 1, 3, 8, 12, 24 hour post-dose
Week 15, 30	All animals in Group 1, 2, 3, 4 and 5	Pre-dose
Days 281, 288, 295, 302	Recovery animals (Group 2, Group 5)	One sample from each day

The plasma minocycline concentrations were determined using a validated LC-MS/MS assay with a lower limit of quantitation of 0.500 ng/mL.

There were no meaningful sex differences in Week 4, Week 20, and Week 39 minocycline TK parameters (Table 3), given the small magnitude of the differences in C_{max} and AUC_{last} and the high variability with overlapping standard deviations in parameter distributions. Therefore, combined-sex minocycline TK parameters were evaluated for each respective TK day.

At Week 4, minocycline systemic exposure after multiple once daily topical application up to 40 mg/kg/day minocycline was observed for all dosed animals at all time points (except one male in group 3 (10 mg/kg/day) at 24-hour post-dose) with a mean minocycline C_{max} of 24.1 ng/mL, 26.2 ng/mL, and 105 ng/mL for Group 3 (10 mg/kg/day), Group 4 (20 mg/kg/day) and Group 5 (40 mg/kg/day), respectively. Week 4 T_{max} ranged from pre-dose to 24 hours (range mean: 0.1 – 7.4 hours). Week 4 AUC_{last} was 214 ng•hr/mL, 346 ng•hr/mL, and 1060 ng•hr/mL for Groups 3, 4, and 5, respectively. A dose-proportional increase in minocycline AUC_{last} was evident at Week 4. A 1:2:4-fold increase in FMX-101 dose corresponded to a 1:1.6:5-fold increase in AUC_{last}, but a 1:1.1:4.4-fold increase in C_{max}.

At Week 20, minocycline systemic exposure was similar to that for Week 4 with slight increases in Groups 3 and 4. Systemic minocycline exposure increased less than dose proportionally at Week 20. A 1:2:4-fold increase in FMX-101 dose corresponded to a 1:0.9:2.1-fold increase in C_{max} and a 1:1:2.2-fold increase in AUC_{last}. No significant (>2X) further minocycline systemic accumulation was observed; ratios of Week 20

AUC_{last} to Week 4 AUC_{last} were 1.9, 1.2, and 0.8 for 10, 20, and 40 mg/kg/day, respectively.

At Week 39, similar to Week 20, quantifiable plasma minocycline concentrations were evident in all animals throughout the entire 24-hour TK blood sampling period. Increases in Week 39 C_{max} and AUC_{last} were less than dose proportional. Systemic minocycline exposure (i.e. AUC_{last}) was similar at doses of 10 mg/kg/day and 20 mg/kg/day. There was no evidence of continued accumulation of minocycline after Week 20.

During the 4-week Recovery period, mean plasma minocycline concentration declined by 96% from Week 39 C_{max} levels.

Overall, toxicokinetic parameter analyses in male and female Hanford minipigs following multiple topical administration of minocycline indicated that there were no significant gender differences in TK parameters. Minocycline C_{max} and AUC_{last} during Weeks 4, 20, and 39 increased less than proportionally over the dosage range of 10 to 40 mg/kg/day. In fact, minocycline systemic exposure was comparable at 10 mg/kg/day and 20 mg/kg/day following 4 weeks, 20 weeks, and 39 weeks of repeated once-daily topical application. After 39 weeks of once daily topical minocycline hydrochloride foam application, minocycline systemic exposure was greatest at 40 mg/kg/day. Minocycline accumulation was minimal at 20 weeks relative to 4 weeks of treatment and no further accumulation occurred beyond 20 weeks. Minocycline systemic exposure persisted, albeit at diminishing concentrations, over the 4-week recovery period following cessation of once-daily topical application of 40 mg/kg/day for 39 weeks.

Table 3 **Mean Plasma Minocycline Toxicokinetic Parameters During Weeks 4, 20 and 39 of Once-Daily Topical Application of Minocycline at 10, 20, and 40 mg/kg/day**

Week	Group	Minocycline (%)	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hour)	AUC_{last} (ng·hr/mL)
4	3	4	10	M	20.9	2.0	209
				F	27.3	2.3	219
				M&F	**24.1**	**2.1**	**214**
	4	8	20	M	32.0	2.0	378
				F	20.5	12.8	313
				M&F	**26.2**	**7.4**	**346**
	5	16	40	M	83.5	0.0 (Pre-dose)	764
				F	127	0.2	1370
				M&F	**105**	**0.1**	**1060**
20	3	4	10	M	41.9	3.0	439
				F	40.5	3.0	379
				M&F	**41.2**	**3.0**	**409**
	4	8	20	M	23.4	5.3	334
				F	47.2	4.3	502
				M&F	**35.3**	**4.8**	**418**
	5	16	40	M	91.7	2.5	883
				F	85.0	2.3	909
				M&F	**88.4**	**2.4**	**896**
39	3	4	10	M	42.1	2.5	478
				F	22.7	1.5	299
				M&F	**32.4**	**2.0**	**388**
	4	8	20	M	14.7	5.0	286
				F	30.5	2.5	417
				M&F	**22.6**	**3.8**	**351**
	5	16	40	M	94.6	1.0	1230
				F	70.4	3.0	1090
				M&F	**82.5**	**2.0**	**1160**

Table 4 Week 20 and Week 39 to Week 4 Dose Proportionality Assessment and Minocycline Exposure Ratios

Week		4			20			39		
Group		3	4	5	3	4	5	3	4	5
Minocycline (%)		4	8	16	4	8	16	4	8	16
Dose Amount (g/kg/day)		0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Dose Area (%BSA)		10			10			10		
Dose Level (mg/kg/day)		10	20	40	10	20	40	10	20	40
Dose Proportionality	Dose Level	1	2	4	1	2	4	1	2	4
	Mean C_{max}	1	1.1	4.4	1	0.9	2.1	1	0.7	2.5
	Mean AUC_{last}	1	1.6	5.0	1	1.0	2.2	1	0.9	3.0
Parameter Ratio	Mean C_{max}	NA			1.7	1.3	0.8	1.3	0.9	0.8
	Mean AUC_{last}				1.9	1.2	0.8	1.8	1	1.1

Dosing Solution Analysis

All test article formulations were analyzed before the first dose administration with one set verified post the last dose administration to verify potency over the period of use. All test article formulations were determined to be in accordance with products specifications. The results are summarized in the following table.

Table 5 Summary of Test Article Formulation Analysis

Formulation	Batch #	Analysis Post Manufacture		Analysis Post Last Dose Administration	
		% of label claim	Date CofA Issued	% of label claim	Date CofA Issued
FMX-101 Vehicle	5091401	No API	08-Feb-2016	NA	NA
	603801	No API	27-Apr-2016	NA	NA
FMX-101 4%	5111801	(b) (4)	08-Feb-2016	NA	NA
	6031601		19-Apr-2016	(b) (4)	11-May-2017
FMX-101 8%	5111601		08-Feb-2016	NA	NA
	6031001		11-May-2016	(b) (4)	11-May-2017
FMX-101 16%	5102201		08-Feb-2016	NA	NA
	6031401		11-May-2016	(b) (4)	11-May-2017

7 Genetic Toxicology

The following information is included in the Solodyn label.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis—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.

8 Carcinogenicity

The following information is included in the Solodyn label.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis— 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.

The sponsor was advised during Pre-IND meeting: "You should adequately address the dermal carcinogenic potential of your topical drug product prior to a NDA submission. It might be possible to request a waiver for conduct of a dermal carcinogenicity study if no preneoplastic/hyperplastic lesions are noted in the 9 month dermal minipig study. If you intend to request a waiver for conduct of a dermal carcinogenicity study with your topical drug product, then you would need to provide an adequate scientific rationale with supporting data to the IND for review." Similar comment was relayed to the sponsor during an End-of- Phase-2 meeting.

The sponsor submitted a waiver request for conduct of a dermal carcinogenicity study with its product, FMX-101. This reviewer recommends that the sponsor's request for a waiver for the conduct of a dermal carcinogenicity study with FMX-101 be granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs.

9 Reproductive and Developmental Toxicology

The following information and statements are included in the Solodyn label.

5. WARNINGS AND PRECAUTIONS

5.1 Teratogenic Effects

A. MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS DRUGS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS.

SOLODYN should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child [see Nonclinical Toxicology (13.1) and Use in Specific Populations (8.1)].

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D [see Warnings and Precautions (5.1)]

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).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

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.

10 Special Toxicology Studies

No special toxicology studies were submitted. A guinea pig dermal sensitization study and an in vitro ocular irritation study with bovine cornea (bovine corneal opacity and permeability assay) are planned by the sponsor but have not been submitted to the IND yet.

The following information and statements are included in the Solodyn label.

5.8 Photosensitivity

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 (tanning beds or UVA/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.

11 Integrated Summary and Safety Evaluation

Minocycline (hydrochloride) is a semi-synthetic derivative of tetracycline. Its oral dosage form is prescribed for the treatment of acne. Minocycline hydrochloride is available in several oral formulations under the brand names Dynacin®, Minocin®, Myrac®, and Solodyn®. Solodyn® (Minocycline Hydrochloride) Extended-Release Tablets was approved by the FDA in 2006 for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

The sponsor is developing its drug product, FMX-101 (minocycline hydrochloride foam, 4%), for topical treatment of (b) (4) inflammatory lesions of non-nodular

moderate to severe acne vulgaris in patients (b) (4) years of age and older. The initial IND was submitted on February 13, 2015. An End-of-Phase 2 meeting was conducted between the Agency and the sponsor on February 17, 2016.

The sponsor requests a waiver for conduct of a dermal carcinogenicity study with its product, FMX-101, under this submission.

The Sponsor intends to rely on the Agency's previous findings of safety for the listed drug (Solodyn® [Minocycline Hydrochloride] Extended-Release Tablets) to support the submission of a 505(b)(2) New Drug Application (NDA) for FMX-101 minocycline hydrochloride foam. The sponsor has conducted two maximal use studies to evaluate the safety and tolerability of FMX101 and to characterize minocycline pharmacokinetics (PK) in adults and pediatrics. The PK data from those studies will be used to establish a clinical bridge to Solodyn® (minocycline HCl) Extended Release Tablets.

According to the Solodyn label, minocycline was not mutagenic in a battery of in vitro and in vivo genetic toxicity studies.

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.

The sponsor submitted a 39-week dermal toxicity minipig study to support its request for a waiver for conduct of a dermal carcinogenicity study with its product, FMX-101, under this submission.

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). 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 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 signs of illness or adverse reaction including at the dose sites. The NOAEL for both local and systemic toxicity 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) based on the results from this study. The C_{max} and AUC_{last} values associated with this NOAEL were 82.5 ng/mL and 1160 hr*ng/mL.

This reviewer recommends that the sponsor's request for a waiver for conduct of a dermal carcinogenicity study with FMX-101 be granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs.

12 Appendix/Attachments

N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renqin DUAN
01/04/2018

BARBARA A HILL
01/04/2018

PHARMACOLOGIST REVIEW OF GLP EIR (CP (b) (4))

Firm Name: (b) (4)
City, State, Country:
EI Dates:
FDA Participants:

Inspection Summary:
This was a FY2017 CDER GLP surveillance inspection. The current inspection covered studies S12917, (b) (4). No Form FDA 483 was issued at the inspection close-out. The final classification is No Action Indicated (NAI). I recommend that the audited studies and other studies of similar design conducted at (b) (4) be accepted for review by the Agency.

Studies Audited during this Inspection:

SRC Study No.:	**S12917**
Study Title:	A 12-Week Dermal Toxicity Study of FMX-101 Foam with 4-Week Recovery in Hanford Minipigs
Study Initiation Date:	(b) (4)
Final Report Date:	
Study Director:	
IND#:	122770
Review Division:	DDDP

(b) (4)

Background: (b) (4) employing approximately (b) (4) persons, is a contract

research organization engaged in biomedical research using large and small animal species. Approximately 40% of the site's workload is subject to part 21 CFR part 58 GLP regulations. Approximately 90% of the GLP studies are related to human drugs.

Prior Inspection: The last FDA GLP Inspection, conducted as directed by the Center for Veterinary Medicine between (b) (4) was classified OAI. An 8-item Form FDA 483, Inspectional Observations, was issued.

Current Inspection: This was a FY2017 GLP Surveillance Inspection conducted by ORA Investigator (b) (4). During the inspection, the following areas were covered: organization and personnel, facilities and facility operations, animal care, equipment calibration and maintenance, SOPs, reagents and solutions, archives, training, and the quality assurance unit activities. The current inspection also covered studies S12917, (b) (4). No objectionable conditions were observed and Form FDA 483 was not issued. The current inspection also verified the corrective actions of the observations from the 2015 inspection.

Recommendations:

- I recommend that the data from the audited studies be accepted for Agency review. Also, the data from studies with similar design conducted before the end of the surveillance interval should be accepted for Agency review.
- This site should be re-inspected in 3 years as part of the CDER GLP surveillance program.
- Final classification: No Action Indicated (NAI).

Mark J. Seaton, Ph.D, DABT
Regulatory Officer

Date Assigned:
EI Dates:
District Office:
FDA Investigators: (b) (4)

Inspection Type: ___X___Routine Surveillance_____Directed
FDA-483 Issued: ___X___No _____Yes
Letter Issued: ___X___None _____Response Request Letter

Date EIR Received by OSIS: 10/23/2017
Date EIR Received by Reviewer: 10/23/2017
1st Draft Review Completed: 10/25/2017

Inspection Conclusion: NAI
District Decision: NAI
Final HQ Classification: NAI

cc: via DARRTS

OSIS/Kassim/Nkah/Fenty-Stewart/Miller/Johnson
OSIS/DNDBE/Bonapace/ChenZ/Seaton/Raha
DDDP /Renqin Duan/Pharmacologist (IND 122770)
DDDP/ Pinakini Patel/Regulatory Project Manager (IND 122770)
DMEP/Huiqing Hao/Pharmacologist (IND [redacted])
DMEP/Callie C. Cappel-Lynch/Regulatory Project Manager (IND [redacted])
DPP/Sonia Tabacova/Pharmacologist (IND [redacted])
DPP/Nam Chun/Regulatory Project Manager (IND [redacted]7)
[redacted]
Draft: [redacted] 10/25/2017; ZC 10/25/2017
Edits: CB 10/27/2017
OSIS File: GLP0955
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/GLP Program/ [redacted] / FY2017/REVIEW (EIR COVER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK J SEATON
10/30/2017

ZHOU CHEN
10/30/2017

CHARLES R BONAPACE
10/31/2017