NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209521
Priority or Standard	Standard
Submit Date(s)	20-OCT-2017
Received Date(s)	20-OCT-2017
PDUFA Goal Date	20-OCT-2018
Division/Office	Division of Dermatology and Dental Products/ODE3
Review Completion Date	27-Sep-18
Established Name	Sarecycline
(Proposed) Trade Name	SEYSARA
Pharmacologic Class	Tetracycline antibiotic
Code name	WC3035
Applicant	Allergan, Inc.
Formulation(s)	Tablets
Dosing Regimen	60 mg, 100 mg, 150 mg
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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
PLT=Patient Labeling Team
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
AQL	acceptable quality limit
BCS	biopharmaceutical classification system
BLA	biologics license application
BMI	body mass index
BOCF	baseline observation carried forward
CAC	carcinogenicity assessment committee
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CPK	(blood) creatine phosphokinase
CRF	case report form
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EOP2	end-of-phase 2
ER	exposure-response
FDA	Food and Drug Administration
HDPE	high-density polyethylene
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IND	Investigational New Drug
iPSP	initial pediatric study plan
IR	immediate release
ITT	intent-to-treat
LC/MS	liquid chromatography/mass spectrometry
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation

PeRC	Pediatric Research Committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population PK
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SOC	standard of care
SPA	special protocol agreement
SMQ	standardized MedDRA query
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Allergan Inc. (the Applicant) submitted New Drug Application (NDA) 209521 for SEYSARA® (sarecycline hydrochloride) 60 mg, 100 mg, and 150 mg in an oral tablet formulation (b) (4)

Sarecycline is a novel tetracycline-class narrow spectrum antibiotic developed for potential treatment of acne vulgaris. Sarecycline exhibits antibacterial activity against clinical isolates of *Propionibacterium Acnes* (*P. acnes)*, including isolates with high-level resistance to the macrolide erythromycin. Activity was also seen for some other Gram-positive species, but unlike other tetracyclines, sarecycline demonstrated little or no activity for the enteric Gram-negative bacilli *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*). In common with other tetracyclines, the antimicrobial action of sarecycline is mediated via inhibition of protein synthesis in *P. acnes*. Sarecycline's narrow spectrum of activity may result in more limited disturbance of gastrointestinal flora when compared with doxycycline and minocycline.

Sarecycline capsules, an immediate-release formulation, were used in phase 1 and phase 2 studies. Warner Chilcott (the original sponsor) developed an immediate-release tablet for the phase 3 clinical studies; equivalence pharmacokinetic (PK) data were provided between the capsules and the tablets. The tablets are the to-be-marketed formulation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Two multicenter, randomized, double-blind, placebo-controlled, pivotal phase 3 clinical trials compared sarecycline tablets (60 mg, 100 mg, and 150 mg) and placebo tablets administered orally once daily for 12 weeks in a total of 2002 patients (intent-to-treat [ITT] population) 9 to 45 years of age with moderate to severe acne vulgaris (Studies SC1401 and SC1402).

The (b) (4) protocols for the phase 3 trials specified that the co-primary efficacy endpoints were: (1) absolute change from baseline in inflammatory lesion counts at Week 12; and (2) the proportion of subjects with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-point decrease from baseline at Week 12. It should be noted that the IGA scale was based only on inflammatory lesions. In addition, for enrollment in the trials, the protocols specified subjects have 20 to 50 inflammatory lesions, up to 100 non-inflammatory lesions, and an IGA score ≥3 (moderate). The Agency recommended (advice letter sent on August 20, 2015) that the phase 3 trials be designed to show lack of worsening in non-

inflammatory lesions and that the trials should include an inclusion criterion for non-inflammatory lesions. The Applicant amended their statistical analysis plan (SAP) for Study SC1401 to add absolute and percent change from baseline in non-inflammatory lesion counts at Weeks 3, 6, 9, and 12 as secondary endpoints after unblinding and analyzing the data from Study SC1402, which had these endpoints designated as "other" secondary endpoints (i.e., these endpoints were not included in the multiplicity testing procedure). The review team is recommending that the indication for this product should be for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older, based on the design and demonstrated outcomes of the clinical trials. Agreement was reached with the Applicant for this indication on September 17, 2018.

In addition, (b) (4) Sarecycline was administered as 60 mg, 100 mg, or 150 mg tablets (body weight-based dose range of 1.1 to 1.8 mg/kg) once daily in subjects who weighed 33 to 54 kg, 55 to 84 kg, and 85 to 136 kg, respectively, in the phase 3 trials. (b) (4) The Agency review team is recommending a weight band dosing for the 60 mg, 100 mg, and 150 mg tablets (b) (4)

In conclusion, sarecycline (tablets, 60mg, 100mg, 150mg) is approvable by weight band dosing for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Allergan Inc. (the Applicant) has submitted NDA 209521 for a drug product, sarecycline 60 mg, 100 mg, and 150 mg, in an oral tablet formulation. The regulatory action pathway for the application is a 505(b)(1). The product is proposed for the indication of once daily oral treatment [redacted] (b) (4) Sarecycline was evaluated in 14 phase 1 clinical studies (in healthy subjects and in patients with impaired hepatic or renal function), as well as a phase 2 dose-ranging study, 2 pivotal phase 3 clinical trials, and a long-term extension safety study in patients with moderate to severe acne vulgaris. Two multicenter, randomized, double-blind, placebo-controlled, pivotal phase 3 clinical trials compared sarecycline tablets (60 mg, 100 mg, and 150 mg) and placebo tablets administered orally once daily for 12 weeks in a total of 2002 patients (ITT population) 9 to 45 years of age with moderate to severe acne vulgaris (Studies SC1401 and SC1402). The pivotal clinical trials enrolled subjects with moderate to severe acne vulgaris (IGA score ≥3 [moderate], 20-50 inflammatory lesions, ≤100 non-inflammatory lesions) with a co-primary efficacy endpoint of absolute change from baseline in inflammatory lesions counts and the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point decrease from baseline at Week 12.

The results for the co-primary efficacy endpoints showed sarecycline was statistically superior to vehicle for both co-primary efficacy endpoints at Week 12.

	Study SC1401			Study SC1402		
Endpoint	**Sarecycline (N=483)**	**Placebo (N=485)**	**P-value**	**Sarecycline (N=519)**	**Placebo (N=515)**	**P-value**
IGA of 0 or 1	21.9%	10.5%	<0.001	22.6%	15.3%	0.004
Absolute Change (Reduction) in Inflammatory Lesion Counts: Mean	15.3	10.2	<0.001	15.5	11.1	<0.001

Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets (MI).

Pooled safety data included all subjects receiving sarecycline; N=2133 total (sarecycline N=1064 and N=1069 for placebo). 295 of 1064 patients (27.7%) receiving sarecycline and 312 of 1069 patients (29.2%) receiving placebo reported at least 1 treatment emergent adverse event (TEAE). The most common TEAEs were headache (3.1% in sarecycline versus 4.3% in placebo), nasopharyngitis (2.8% versus 2.6%), nausea (3.1% versus 2.0%), upper respiratory tract infection (1.6% versus 1.5%), blood creatine phosphokinase (CPK) increased (1.2% versus 1.3%), diarrhea (1.0% versus 1.3%), vomiting (1.3% versus 0.9%),

oropharyngeal pain (1.0% versus 0.9%), urinary tract infection, dizziness, and cough (each 0.5% versus 1.0%). Vulvovaginal mycotic infections and vulvovaginal candidiasis were ≤1% and more frequent in sarecycline-treated females (0.8% [5 of 618]) than in placebo (0 of 610). Vestibular TEAEs (dizziness, vertigo, tinnitus, nausea, and vomiting) occurred more frequently in the sarecycline group [4.5% (48 patients)] compared with the placebo [3.5% (37 patients)]. Tinnitus did not occur in either treatment group. The incidences of treatment-emergent serious adverse events (SAEs) were similar in the sarecycline and placebo groups (0.7% versus 0.6%, respectively). Similarly, the incidence of TEAEs that led to patient discontinuation was the same in both treatment groups (1.3%). The open-label long-term extension study provided supportive safety data. Sarecycline, as a tetracycline class antibiotic, should not be used in children ≤8 years of age due to risk of permanent discoloration of teeth and interference with bone growth/formation. Sarecycline should not be taken during pregnancy or breastfeeding.

The Agency discussed (b) (4) Furthermore, the proposed doses of sarecycline were demonstrated to be effective and had acceptable safety in the phase 3 trials. Therefore, the Applicant's proposed dosing regimen (i.e., 60 mg, 100 mg, or 150 mg once daily for patients who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively) is appropriate.

The Applicant has demonstrated that sarecycline is safe and effective for the treatment of inflammatory lesions of acne vulgaris in subjects 9 years of age and older. The dosing is based on the weight table provided in the Prescribing Information (PI). From a clinical perspective, it is recommended that the Application be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acne vulgaris is a chronic disease of pilosebaceous follicles that is multi-factorial in etiology and characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulo-cystic lesions). Acne vulgaris has its onset in puberty, but may persist past the third decade of life, and it affects all races. • In clinical practice, the choice of treatment depends on the type, number, and severity of skin lesions present. Common treatments for inflammatory acne are topical and oral tetracyclines. Sarecycline is a narrow spectrum antimicrobial agent that is purported to reduce the colonization of *P. acnes*, the predominant bacterium associated with lesion inflammation, within sebaceous follicles.	Acne is a common condition in children and adults. The choice of treatment is a clinical choice made by the physician and the patients and depends on type, severity, and location of lesions. Sarecycline is a narrow spectrum acne product that would be an addition to the armamentarium of acne treatment options for moderate to severe inflammatory acne. No antimicrobial claims are asserted
Current Treatment Options	• Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies include oral and topical antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide), systemic hormonal therapies (e.g., ethinyl estradiol/norgestimate), and topical retinoids (e.g., tretinoin, tazarotene). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.	Sarecycline represents another available treatment for this condition.
Benefit	• In clinical trials, oral sarecycline was effective in the treatment of moderate to severe inflammatory acne vulgaris in patients 9 years of age and older.	The beneficial effects of sarecycline treatment in inflammatory acne have been demonstrated across two placebo-controlled clinical trials.
Risk	• In clinical trials, oral sarecycline was well tolerated in patients with moderate to severe inflammatory acne vulgaris, 9 years of age and older. The long-term, open-label study did not reveal any significant safety issues.	Sarecycline was determined to be safe and well-tolerated for the overall populations enrolled in clinical trials and for all evaluated demographic subgroups.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There were no adverse effects with kidney or liver dysfunction in clinical studies. • Known adverse events related to tetracycline antibiotics include gastrointestinal upset, esophageal erosion, fungal infection, increased photosensitivity, and permanent discoloration of teeth and interference with bone growth/formation in children. • Tetracycline class antibiotics are contraindicated in pregnancy and breastfeeding, and should not be given to children ≤8 years of age. • Antibiotic-associated diarrhea has been reported with certain antibacterial agents, including tetracyclines. • Benign intracranial hypertension in adults has been associated with use of tetracyclines.	The safety profile for sarecycline is generally similar to that of other tetracycline class antibiotics.
Risk Management	• A risk evaluation and mitigation strategy (REMS) is not recommended for sarecycline.	Labeling is sufficient to manage the risks associated with sarecycline.

1.4. Patient Experience Data

Patient experience data pertaining and submitted with this application are outlined in Table 1.

Table 1: Patient Experience Data Relevant to this Application

x	The patient experience data that were submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	SC1401, SC1402
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	SC1401, SC1402
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)		
	□	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 chronic disease of pilosebaceous follicles that is multi-factorial in etiology and characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulo-cystic lesions).[1] Acne vulgaris has its onset in puberty but may persist past the third decade of life, and it affects all races.

2.2. Analysis of Current Treatment Options

A number of topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies include oral and topical antibiotics and antimicrobials (See Table 2, Table 3, and Table 5) (e.g., erythromycin, clindamycin, benzoyl peroxide), systemic hormonal therapies (see Table 6) (e.g., ethinyl estradiol/norgestimate), and topical retinoids (see Table 4) (e.g., tretinoin, tazarotene). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

Table 2: Topical Antimicrobials

Medications	Dose	List of Preparations
Benzoyl peroxide†	Twice daily	Multiple 2.5% to 10% gels, lotion, creams, pads, masks, cleansers
Clindamycin	Twice daily	1% gel, lotion, solution, foam
Erythromycin	Twice daily	2% gel, solution
Dapsone	Twice daily	5% gel
Sodium sulfacetamide (KLARON®)	Twice daily	10% lotion, wash, suspension, pad plus 10% urea

Source: Adapted from a previous clinical review Gary Chiang MD, MPH
† Benzoyl peroxide is non-prescription

[1] Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis-related treatment of acne. *J Dermatol*. 1991;18:489-99.

Table 3: Topical Combination Products

Medications	Dose	List of Preparations
Benzoyl peroxide 5% - Clindamycin 1% (BENZACLIN® and DUAC®)	Twice daily	Gel
Benzoyl peroxide 5% - Erythromycin 3% (BENZAMYCIN®)	Twice daily	Gel
Benzoyl peroxide 2.5% - Clindamycin 1.2% (ACANYA®)	Once daily	Gel
Clindamycin 1.2% - Tretinoin 0.025% (ZIANA®)	Once daily, at bedtime	Gel
Benzoyl peroxide 2.5% - Adapalene 0.1% (EPIDUO®)	Once daily	Gel
Azelaic acid (FINACEA® and AZELEX®)	Twice daily	20% cream, 15% gel

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

Table 4: Retinoids (Topical and Oral)

Medications	Dose	List of Preparations
Topical Retinoids		
Tretinoin	Once daily, at bedtime	Creams: 0.025%, 0.05%, 0.1% Gels: 0.01%, 0.025%, 0.05% Microsphere gels: 0.04%, 0.1% Prepolyolprepolymer gel: 0.025%
Adapalene	Once daily, at bedtime	Cream: 0.1% Gels: 0.1%, 0.3%
Tazarotene	Once daily, at bedtime	Creams: 0.05%, 0.1% Gels: 0.05%, 0.1%
Oral Retinoid		
Oral isotretinoin	0.5mg/kg/day, increasing to 1mg/kg/day; total dose 120 to 150mg/kg over 20 weeks	Oral

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

Table 5: Oral Antibiotics

Medications	Dose
Tetracycline	500mg twice daily
Doxycycline	50 to 100mg twice daily or 150mg once daily
Minocycline	50 to 100mg twice daily or 1mg/kg.day or the extended release formulation
Erythromycin	500mg twice daily
Trimethoprim-sulfamethoxazole	160mg/800mg once to twice daily
Azithromycin [a]	Intermittent dosing due to long drug half-life; optimum regimen unknown

Source: Adapted from a previous clinical review Gary Chiang MD, MPH
Note: Antibiotics are frequently used in clinical practice but may not be approved for the indication.
[a] Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95.

Table 6: Hormonal Agents

Medications	Dose
Combination oral contraceptives (estrogen/progestin)	Once daily
Spironolactone	25 to 200mg/day; doses of 50 to 100mg/day may be as effective as higher doses and reduce side effects

Source: Adapted from a previous clinical review Gary Chiang MD, MPH

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This drug product is not marketed in the United States or other countries.

3.2. Summary of Presubmission/Submission Regulatory Activity

Multiple meetings were held with the original sponsor (Warner Chilcott) to discuss the development of WC3035 for the treatment of acne. On September 6, 2011, the sponsor requested a Type B guidance meeting. The briefing package included a phase 2 clinical protocol (PR-10411.0) evaluating 3 doses of study drug WC3035 (3.0 mg/kg/day, 1.5 mg/kg/day, and 0.75 mg/kg/day). Written responses to the sponsor's submitted questions were relayed on January 20, 2012. On April 23, 2014, the Agency held an end-of-phase 2 (EOP2) meeting with the sponsor; however, after receiving the pre-meeting communication, the sponsor determined that the Agency's responses to their questions were sufficient and the sponsor cancelled the meeting. In the responses, the Agency recommended conducting another phase 2 dose-ranging study to determine the optimal dose for this drug product and we pointed out that the completed phase 2 study to date lacked a clear dose response relationship and therefore may not represent the "optimal" dosing regimen for a phase 3 clinical trial:

> *"Our meeting responses are based on the briefing document and we have not completed review of your final study report of the Phase 2 dose ranging trial. We are concerned that we have identified certain issues that may impact the conclusion that treatment effects of your proposed dosing regimen have been adequately evaluated in Phase 2. We are not confident that you have identified a dosing regimen most likely to succeed in Phase 3.*
>
> *The impact of subject outliers, the applicability of fixed dose regimen in your Phase 2 trial to the weight-based dosing in Phase 3, and the variable success rates according to subject baseline disease severity lead us to recommend additional Phase 2 dose ranging prior to agreements on your Phase 3 trials."*

The sponsor used a fixed dose regimen in their phase 2 trial; however, the sponsor proposed to use weight-based dosing in their phase 3 trials. The EOP2 meeting package did not contain the sponsor's rationale for switching from a fixed dosing regimen to one based on weight. In addition, the meeting package did not contain any results for an investigation of the relationship between efficacy and weight-based dosing (i.e., assigned fixed dose (50, 100, 200 mg) divided by subject's body weight).

On May 16, 2014, the sponsor submitted a Special Protocol Agreement request (SPA) for their phase 3 studies. The SPA was denied by the Agency on concerns by the

Division at the EOP2 meeting that the sponsor's phase 2 dose-ranging study was insufficient; thus, agreements regarding the phase 3 study design were not reached.

On January 6, 2017, the Agency provided premeeting comments to the sponsor, the pre-NDA meeting was cancelled as the sponsor was satisfied with the Agency's written comments. In response to their statistical plan, the Agency reiterated that "You do not plan to conduct any analyses for non-inflammatory lesions. Your application should include analyses for non-inflammatory lesions to determine whether there is worsening in non-inflammatory lesions with the application of your product. In addition, your application should include the non-inflammatory lesion count data."

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

4.1. Office of Scientific Investigations

OSI conducted three inspections for the Phase 3 clinical trials conducted for sarecycline. Tory Cyllican, MD, PA in Miami Beach, Florida (SC1401), Sanjeev Sharma, MD in Oceanside, California (SC1402), and Eduardo Tschen, MD, MBA in Albuquerque, New Mexico (SC1402) was reviewed for their conduct in the clinical investigations. All three inspections did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Recommendations and Conclusion on Approvability
The Applicant of this NDA has provided sufficient chemistry, manufacturing, and controls (CMC) information to assure the identity, strength, purity, and quality of the drug substance and drug product. The facility review team from the Office of Process and Facility has issued an "Acceptable" recommendation for the facilities involved in this application. The revised Prescribing Information and mock-up container and carton labels are deemed satisfactory from the CMC perspective. From the Office of Pharmaceutical Quality (OPQ) perspective, this NDA is recommended for approval.

Summary of Quality Assessments

Drug Substance:

The active pharmaceutical ingredient (API) in sarecycline tablets is sarecycline hydrochloride, (b) (4) The chemical name for sarecycline hydrochloride is (4S,4aS,5aR,12aS)-4-(Dimethylamino)-3,10,12,12a-tetrahydroxy-7-[(methoxy-(methyl)-amino)-methyl]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrochloride. The chemical structure of sarecycline hydrochloride is:

It has a molecular formula of $C_{24}H_{29}N_3O_8 \cdot HCl$ and a molecular weight of 523.96 g/mol. Sarecycline hydrochloride is a yellow to slightly green powder. It is sparingly soluble in water and methanol, slightly soluble in ethanol, and practically insoluble in acetonitrile. Its aqueous solubility increases with increasing pH (226 mg/mL at pH 8.0). It has pKa values of 2.03, 3.30, 7.60, and 9.92. It is sensitive to light and slightly hygroscopic.

The drug substance manufacturing process has been modified and optimized (b) (4) The source and fate of potential organic impurities including mutagenic and genotoxic impurities are discussed. The levels of organic and inorganic impurities and residual solvents are monitored and controlled in the drug substance specification. The identity, purity, strength, and quality of the drug substance are adequately assured by the drug substance specification. All non-compendial test methods used for drug substance assay, and its related substances, genotoxic impurities (b) (4) elemental impurities, and residual solvents present in the drug substance were properly validated.

The drug substance is packaged (b) (4) The proposed retest period of (b) (4) months for the drug substance when stored (b) (4) is supported by the stability data provided. The NDA is recommended for approval from the drug substance perspective.

Drug Product:

The drug product is available in 3 different strengths, 60 mg, 100 mg, and 150 mg. The API used in the tablets is sarecycline hydrochloride. The 60 mg tablets are capsule-shaped, yellow, film-coated tablets debossed with “S60” on one side and blank on the other side. The 100 mg tablets are capsule-shaped, yellow, film-coated tablets debossed with “S100” on one side and blank on the other side. The 150 mg tablets are capsule-shaped, yellow, film-coated tablets debossed with “S150” on one side and blank on the other side. The inactive ingredients used in the drug product include microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate. The yellow film coating (b) (4) contains D&C yellow #10

aluminum lake, iron oxide yellow, methacrylic acid copolymer type C, polyethylene glycol, polyvinyl alcohol, sodium bicarbonate, talc, and titanium dioxide. There are no novel excipients or excipients of human or animal origin. All excipients are commonly used in oral tablet dosage forms.

Thirty tablets are packaged in 60 cc square HDPE bottles with a 33 mm child resistant [redacted] cap [redacted] Three tablets of the drug product are packaged in 30 cc round white HDPE bottles with a 28 mm child resistant [redacted] cap [redacted] All batches of the drug product met release specification and confirmed batch-to-batch consistency for release testing of the drug product. The drug product specification for sarecycline tablets is deemed adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period.

Stability studies were conducted on 9 batches (3 batches for each tablet strength) of the drug product manufactured at [redacted] with the drug substance produced [redacted] Stability studies were also conducted on 3 registration batches (1 batch for each tablet strength) of the drug product manufactured [redacted] with the drug substance produced [redacted] Based on the available stability data of the drug product, a 24-month expiration dating period is recommended for sarecycline tablets, 60 mg, 100 mg, and 150 mg in the commercial packaging configurations when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). The estimated expected introduction concentration for the active moiety of the drug substance is [redacted] ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31(b). The NDA is recommended for approval from the drug product perspective.

Labeling and Labels:

The revised PI and mock-up container, carton, and tray labels are deemed satisfactory from the CMC perspective.

Drug Product Manufacturing Process:

The proposed drug product, sarecycline tablets, is manufactured by a [redacted]

The batch formula, manufacturing process parameters, and in-process controls are deemed adequate to ensure the robustness of the drug product manufacturing process. The proposed manufacturing process, batch size (b) (4) and facility for intended commercial batches are the same as those used for manufacturing the registration batches of the drug product. The NDA is recommended for approval from the perspective of drug product manufacturing process.

Biopharmaceutics:

The Applicant is seeking approval of sarecycline oral tablets for the treatment inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. The API is a tetracycline-class narrow spectrum antibiotic which exhibits antibacterial activity against clinical isolates of *P. acnes*. The immediate release (IR) film-coated tablets contain 60 mg, 100 mg, or 150 mg of sarecycline (equivalent to 64.5 mg, 107.5 mg, and 161.2 mg of sarecycline hydrochloride, respectively). The proposed dose of the drug is (b) (4) once daily. According to the information provided by the Applicant, sarecycline hydrochloride is rapidly absorbed

following oral administration of the IR tablet formulation and displays linear and near dose-proportional pharmacokinetics within the range of 60 to 150 mg dosed once daily (QD).

Based on a reported permeability and solubility study performed over a physiological pH range, as per the Biopharmaceutical Classification System (BCS), sarecycline hydrochloride can be classified as a BCS Class III compound. According to the Applicant (b) (4)

The drug product underwent some major CMC changes during the development program. Of relevance is a change in formulation from phase 1 (capsules) to phase 2 (film-coated tablets). The change in formulation and dosage form did not affect the in vivo performance of the product as demonstrated by the results of a bioequivalence study. The formulation used in the pivotal phase 3 studies is the same as the intended commercial one. No changes in manufacturing site for the drug product occurred from phase 3 to commercial production.

The *in vitro* release test method is summarized in the following Table 7.

Table 7: Parameters of Dissolution Test Method

Test Parameter	Setting
Apparatus	USP Apparatus 2 - Paddle
Rotation speed (rpm)	75
Dissolution medium	0.1 N HCl
Medium Volume	500 mL
Medium Temperature	37°C±0.5°C

The acceptance criterion of the dissolution test is NLT (b) (4)% (Q) in 15 minutes.

The NDA is recommended for approval from the perspective of biopharmaceutics.

Quality Microbiology:

The drug product is in the form of IR oral tablets. Microbial limit tests, which include tests of total aerobic microbial count, total combined yeasts and molds count, and the test for *E. coli*, are included in the drug product specification.

Microbial examination was performed on the registration batches of sarecycline tablets as per USP <61> and <62> at release. All tested batches conformed to the specification limits. (b) (4)

(b) (4)

The NDA is recommended for approval from the perspective of quality microbiology.

Facilities:
The status of the facilities related to the drug substance manufacture and testing is summarized in Table 8:

Table 8: Status of Facilities Related to Drug Substance Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)		Drug substance manufacture, release and stability testing (b) (4)	Acceptable
		Drug substance testing (b) (4) (CTL)	Acceptable

The status of the facilities related to the drug product manufacture and testing is summarized in the following Table 9:

Table 9: Status of the Facilities Related to the Drug Product Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)		Drug product manufacturing (TCM)	Acceptable
		Drug product packaging (TCM)	Acceptable

All the facilities are deemed acceptable in their identified functions and responsibilities to support the approval of NDA 209521.

Clinical Microbiology

No clinical microbiology assessments were included in the development program. No labeling claims are asserted, and none are supported in this application.

4.3. Devices and Companion Diagnostic Issues

None.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sarecycline is a tetracycline-class antibiotic. Sarecycline demonstrated antibacterial and anti-inflammatory activities in pharmacology studies. In single oral dose safety pharmacology studies conducted with sarecycline, reductions in locomotor activity were noted in rats at doses ≥300 mg/kg. Decreases in respiratory rate and increases in tidal volume were observed in rats at 2,000 mg/kg. Decreases in blood pressure were noted in monkeys at 400 mg/kg.

Repeat-dose oral toxicity studies were conducted in mice, rats, and monkeys. Major target organs of toxicity were identified as liver and kidney. Bone and tooth discoloration (an expected effect of tetracyclines) and pigment deposition in thyroid gland were not considered toxicologically adverse. Major histopathological findings included centrilobular hepatocellular vacuolation (in mice, rats, and monkeys) and papillary necrosis in kidney (in mice and rats). The NOAELs identified in the 26-week rat study and 39-week monkey study were 50 and 150 mg/kg/day, which are 5.2 and 3.6 times the maximum recommended human dose (MRHD), respectively, based on AUC comparisons.

In genetic toxicology studies, sarecycline was negative in a bacteria reverse mutation assay, an in vitro chromosomal aberration test in Chinese hamster ovary cells, the L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay, and an in vivo micronucleus assay in rats.

Two-year oral carcinogenicity studies were conducted in mice and rats. Both studies were adequately conducted. For both studies, a complete list of tissues was examined histopathologically. There were no significant test article-related neoplastic findings in either study. Adverse non-neoplastic histopathological findings were noted in the kidney (papillary necrosis) at high dose in both studies. The high doses of the two studies, 100 mg/kg/day in male mice, 60 mg/kg/day in female mice, and 200/100 mg/kg/day in rats, are 1.2, 0.9, and 7.5 times the MRHD, respectively.

In a fertility study, sarecycline was administered to both male and female rats prior to pairing and through the mating and postmating period, at oral doses up to 400 mg/kg/day. There were no significant findings in females. In sperm evaluation, decreased sperm motility, decreased sperm count and concentration, and an increase in percent abnormal sperm were observed at 400 mg/kg/day. The NOAEL for female fertility was 400 mg/kg/day, 7.9 times the MRHD. The NOAEL for male fertility was 150 mg/kg/day, 4 times the MRHD.

Embryofetal development studies were conducted in rats and rabbits. Sarecycline was administered to female rats during the period of organogenesis, at oral doses of 50, 150, and 500 mg/kg/day. A decrease in maternal body weight was noted at the high dose in rats. A decrease in fetal body weight and litter size and an increase in the

number of resorption and post-implantation loss was noted at the high dose in rats. Significant skeletal malformations were observed at all doses in a dose-related manner. Sarecycline was clearly teratogenic in rats under the study conditions. The NOAEL for maternal toxicity was 150 mg/kg/day (2.5 times the MRHD), while a NOAEL for embryofetal toxicity could not be established. Sarecycline was administered to rabbits during the period of organogenesis, at oral doses of 50, 100, and 150 mg/kg/day. Excessive maternal toxicity was noted at the high dose and therefore the high dose animals were terminated early with no litters available for evaluation. Two mid-dose females were euthanized early due to moribundity. The NOAEL for maternal toxicity was 50 mg/kg/day, 0.6 times the MRHD. No significant test article-related developmental toxicity was observed at the low dose or mid dose. The NOAEL for embryofetal toxicity was 100 mg/kg/day, 0.6 times the MRHD.

In a pre- and postnatal developmental study in rats, sarecycline was administered to female rats during the period of organogenesis through lactation, at oral doses of 50, 150, and 400 mg/kg/day. The F1 pups were potentially exposed to the test article in utero and through lactation but were not dosed directly. Excessive litter toxicity was noted at the high dose which led to early termination of F0 dams at parturition. Decreases in body weight and food consumption were noted in mid-dose F0 dams during the lactation period. The NOAEL for maternal toxicity was 50 mg/kg/day, 1.4 times the MRHD. There were decreases in pup survival, pup weight during the preweaning and growth period, and implantation sites and viable embryos (in F1 females). The NOAEL for developmental toxicity was 50 mg/kg/day, 1.4 times the MRHD.

Sarecycline exhibited phototoxicity in hairless mice, which is an expected effect of tetracyclines.

This NDA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical postmarketing commitment (PMC)/postmarketing requirement (PMR) for this NDA.

5.2. Referenced NDAs, BLAs, and DMFs

For pivotal nonclinical data that have been reviewed under Investigational New Drug Application (IND) 107645, summary pharmacology/toxicology information is provided in this review. The code names used for sarecycline hydrochloride were WC3035 and P005672.

5.3. Pharmacology

Primary pharmacology

Sarecycline is a tetracycline-class antibiotic. A number of in vivo pharmacology experiments were conducted with sarecycline using various animal infection models

(including an intraperitoneal infection mouse model, an acute respiratory tract infection mouse model, and a thigh wound infection mouse model) and an inflammation animal model (a carrageenan-induced rat paw edema model). Sarecycline demonstrated antibacterial activity against *Staphylococcus aureus (S. aureus)* and *S. pneumoniae* (Gram-positive) but had no significant activity against *E. coli* (Gram-negative). Sarecycline also demonstrated anti-inflammatory activity in the inflammation animal model.

Secondary Pharmacology

No secondary pharmacology studies were conducted with sarecycline.

Safety Pharmacology

Neurological effects:

Single oral (gavage) doses of 0 (vehicle: 0.5 M sodium phosphate in deionized water, pH 8 ± 0.1), 300, 1000, or 2000 mg/kg sarecycline were administered to male SD rats (16 per group). Ten males per group were designated for neurobehavioral evaluations and 6 males per group were designated for locomotor activity monitoring. No mortality was observed. A decrease in body temperature was noted at the high dose (-0.98°C at 6 hours postdose, -0.68°C at 24 hours postdose). Within 20 to 30 minutes postdose, there were significant reductions in basic movement, fine movement, total distance, and/or rearing counts at all dose levels. These reductions in locomotor activity had resolved by 6 hours postdose for the low- and mid-dose groups and by 24 hours postdose for the high-dose group. No NOAEL was identified in this study based on locomotor activity reduction seen in all dose groups.

Note: The same vehicle (0.5 M sodium phosphate in deionized water, pH 8±0.1) was used in all animal oral toxicology studies described in this review.

Respiratory effects:

Single oral (gavage) doses of 0 (vehicle), 300, 1000, or 2000 mg/kg sarecycline were administered to male SD rats (8 per group). No mortality was observed. Respiratory rate, tidal volume, and minute volume were measured. Decreases in respiratory rate and increases in tidal volume were observed at high dose. The NOAEL for respiratory effects was identified as 1000 mg/kg in this study.

Cardiovascular effects:

A definitive in vitro hERG assay was conducted following a screening assay. Two concentrations of sarecycline (10 and 200 µM) were tested. Higher concentrations were not tested due to solubility limitations. Sarecycline did not significantly inhibit hERG current in this study. The IC_{50} was greater than 200 µM.

Sarecycline was tested for cardiovascular effects in conscious free-moving cynomolgus monkeys. Single oral (gavage) escalating doses of 0 (vehicle), 100, 250, and 400 mg/kg were administered to 4 male monkeys, with a 7- or 8-day washout period between each dose. Cardiovascular parameters, including systolic, diastolic, and mean arterial blood pressures, heart rate, and ECG (including QRS duration and RR, PR, QT, and QTc intervals) were monitored.

There were no observed effects on mortality or body weight. Blood pressure (systolic, diastolic, and mean arterial) in one male at high dose decreased at ~15 to 30 min postdose and returned to control level within 6 hours postdose. At ~2 hours postdose, blood pressure for this animal reached a peak decrease of ~50%. Blood pressure was consistently lower than control for all other animals at the high dose, although at a lesser degree (~5 to 10%) and generally returned to control level or near control level within 18 hours postdose. An increase in heart rate (up to ~30 to 50%) was observed in one male at mid dose and two males at high dose. The increased heart rate returned to control levels or near control levels by 6 hours postdose. In one male at the high dose, RR, PR, and uncorrected QT interval durations were decreased (~20 to 25%), which was consistent with the observed heart rate increase.

The NOAEL for cardiovascular effects was identified as 250 mg/kg in this study, based on the hypotension effect noted at 400 mg/kg.

5.4. ADME/PK

PK/TK data are summarized in Table 10.

Table 10: Summary of PK/TK Data for Sarecycline

Type of Study	Major Findings
Absorption	
Pharmacokinetics of P005672-04 in cynomolgus male monkey (Study# CR-04710.0)	Monkey (single oral dose of 5 mg/kg) $T_{1/2}$: 9.6 hr C_{max}: 2.9 µg/ml T_{max}: 3.0 hr $AUC_{0-\infty}$: 28.7 µg·hr/ml Bioavailability: 78.2%
Distribution	
[^{14}C]-P005672: ADME and metabolism study in rats (Study# CR-02510.0)	Distribution was evaluated in male albino (SD) and pigmented (Lister Hooded) rats following a single oral dose of sarecycline. Highest concentrations of radioactivity were mainly observed in the gastrointestinal tract and bone, with notable concentrations of radioactivity remaining in the periodontal membrane, bone, and thyroid gland at 168 hr postdose in both groups of animals.
In vitro assessment of P005672 and P005697 (epimer of P005672) protein binding in mouse, rat, rabbit, monkey, and human plasma (Study# CR-04013.0)	At concentrations of 0.5 to 50 µg/ml, mean in vitro protein binding of sarecycline in plasma ranged from 55.9% to 65.4% for mouse, 61.4% to 64.6% for rat, 76.2% to 78.9% for rabbits, 66.1% to 71.8% for monkey, and 62.5% to 74.7% for human.
Metabolism	

Type of Study	Major Findings
Mass balance, radio profiling and metabolite ID in cynomolgus monkeys after a single oral dose of [^{14}C]-P005672 (Study# CR-12311.0)	Following a single oral dose of 20 mg/kg ^{14}C-labelled sarecycline to monkeys, 17 metabolites were identified, most of which were formed by O-/N-demethylation, hydroxylation, and/or additional modifications to the N, O-dimethylhydroxylamine moiety. Sarecycline and its 4R-epimer were the predominant circulating components in plasma, accounting for 70.5% and 21.2% of $AUC_{0\text{-}24hr}$, respectively.
Excretion	
Mass balance, radio profiling and metabolite ID in cynomolgus monkeys after a single oral dose of [^{14}C]-P005672 (Study# CR-12311.0)	In the metabolism study with ^{14}C-sarecycline in monkeys, 92.8% of administered radioactivity was recovered, with 79.8% and 7.59% of the dose excreted in feces and urine, respectively.
TK data from general toxicology studies P005672-HCl: A 26-week oral toxicity study in rats with a 13-week recovery (Study# 1753-019) P005672-HCl: A 39-week oral toxicity study in naive monkeys with a 13-week recovery period (Study# 1753-020)	 <u>Rat (oral daily dosing for 6 months)</u> $T_{1/2}$: 2.67-4.27 hr $AUC_{0\text{-}24hr}$ at Week 26 (sex combined): 50 mg/kg/day: 250 µg·hr/ml 150 mg/kg/day: 564 µg·hr/ml 400 mg/kg/day: 663 µg·hr/ml Accumulation: 2.3, 2.9, and 1.8-fold for 50, 150, and 400 mg/kg/day doses comparing AUC at Week 26 to Day 1 Dose proportionality: The AUC increase was less than dose proportional. <u>Monkey (oral daily dosing for 9 months)</u> $T_{1/2}$: 6.21-10.7 hr $AUC_{0\text{-}24hr}$ at Week 39 (sex combined): 50 mg/kg/day: 54.8 µg·hr/ml 150 mg/kg/day: 174 µg·hr/ml 400 mg/kg/day: 628 µg·hr/ml Accumulation: 1.0, 1.4, and 3.0-fold for 50, 150, and 400 mg/kg/day doses comparing AUC at Week 39 to Day 1 Dose proportionality: The AUC increase was less than dose proportional at Day 1 and roughly dose proportional at Week 39.
TK data from reproductive toxicology studies P005672 HCl: An oral study for effects on embryofetal development in rats with a toxicokinetic evaluation (Study# 1753-012) P005672 HCl: An oral study for effects on embryofetal development in rabbits with a toxicokinetic evaluation (Study# 1753-013)	 <u>Maternal Rat (oral daily dosing during gestation days 6-17)</u> $AUC_{0\text{-}24hr}$ (gestation day 17): 50 mg/kg/day: 69.4 µg·hr/ml 150 mg/kg/day: 122 µg·hr/ml 500 mg/kg/day: 342 µg·hr/ml <u>Maternal Rabbit (oral daily dosing during gestation days 7-19)</u> $AUC_{0\text{-}24hr}$ (gestation day 19): 50 mg/kg/day: 27.2 µg·hr/ml 100 mg/kg/day: 31.3 µg·hr/ml 150 mg/kg/day: 247 µg·hr/ml
TK data from carcinogenicity studies P005672-HCl: A 104-week oral	 <u>Mouse (oral daily dosing for 2 years)</u>

Type of Study	Major Findings
carcinogenicity study in mice (Study# 1753-022)	$AUC_{0\text{-}24hr}$ at Week 78: 100 mg/kg/day (male): 56.7 µg·hr/ml 60 mg/kg/day (female): 45.2 µg·hr/ml
P005672-HCl: A 104-week oral carcinogenicity study in rats (Study# 1753-021)	Rat (oral daily dosing for 2 years) $AUC_{0\text{-}24hr}$ at Week 78 (sex combined): 200/100 mg/kg/day: 363 µg·hr/ml

5.5. Toxicology

5.5.1. General Toxicology

Study 1 P005672-HCl: A 12-week oral dose toxicity study in rats with an 8-week recovery period (Study# 1753-008)

Oral (gavage) doses of 0 (vehicle), 15, 30, 60, and 200 mg/kg/day sarecycline were administered to SD rats (10/sex/group) once daily for 12 weeks, followed by an 8-week recovery period (5/sex/group for control and high dose groups). There were no significant test article-related effects on mortality, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, or organ weights. Test article-related macroscopic findings were noted in thyroid glands, femoral bone, and liver. Minimal to severe black, brown, or red discoloration was seen in the thyroid gland at all dose levels. The discoloration in the thyroid gland correlated microscopically with test article-related pigment deposition. Minimal to severe yellow discoloration of femoral bone was seen at all dose levels with a dose-related increase in incidence and severity. The discoloration in the thyroid gland and femoral bone was also seen in recovery animals at high dose.

Test article-related microscopic findings were noted in the liver, mesenteric lymph node, jejunum, ileum, and thyroid gland. Minimal to moderate centrilobular hepatocellular vacuolation was present in the liver in males at all dose levels with a dose-related increase in incidence and severity. This finding was characterized by the presence of numerous small clear intracytoplasmic vacuoles within centrilobular hepatocytes and was not associated with evidence of hepatocellular necrosis. Vacuolation was also noted in the mesenteric lymph node, jejunum, and ileum. There was no associated evidence of cellular necrosis. The thyroid gland of males at all dose levels and females at doses ≥30 mg/kg/day exhibited pigment deposition with a dose-related increase in incidence and severity. This finding was characterized by the presence of brown granular pigment within the apical cytoplasm of follicular epithelial cells and was not associated with evidence of cellular toxicity. After the recovery period, hepatocellular vacuolation was no longer noted. Vacuolation in the mesenteric lymph node, ileum, and jejunum persisted but with no associated evidence of cellular necrosis. Pigment deposition was also noted in the thyroid gland at the high dose and no signs of cellular toxicity were observed.

The doses for the 2-year oral rat carcinogenicity study were selected based on the results of this study.

Study 2 P005672-HCl: A 13-week oral dose toxicity study in mice (Study# 1753-007)

Oral (gavage) doses of 0 (vehicle), 30, 100, and 500/300 mg/kg/day sarecycline were administered to CD-1 mice (12/sex/group) once daily for 13 weeks. Mortality was noted at the high dose (500 mg/kg/day). Consequently, the high dose was lowered to 300 mg/kg/day starting from Day 25. A reduction in body weight gain was noted in mid-dose and high-dose females. No adverse effects on body weight were noted in males. There were no significant test article-related effects on ophthalmology, hematology, clinical chemistry, or gross pathology. Minimal centrilobular hepatocellular vacuolation was noted in 1 mid-dose male and 9 high-dose animals (6 males and 3 females). The hepatocellular vacuolation was not associated with cellular necrosis. One mid-dose male and 2 high-dose males had moderate cystic bile duct hyperplasia. Minimal vacuolation was occasionally present in the mesenteric lymph node and/or ileum of high-dose animals. There was no associated necrosis.

The doses for the 2-year oral mouse carcinogenicity study were selected based on the results of this study.

Study 3 P005672-HCl: A 26-week oral toxicity study in rats with a 13-week recovery period (Study# 1753-019)

Oral (gavage) doses of 0 (vehicle), 50, 150, and 400 mg/kg/day sarecycline were administered to SD rats (20/sex/group) once daily for 26 weeks, followed by a 13-week recovery period (10/sex/group for control, mid-dose and high-dose groups). Mortality/moribundity was noted at the mid dose (2 males) and high dose (4 males and 4 females). The deaths were mainly due to pulmonary lesions consistent with dosing injury. Hemorrhage and subacute/chronic inflammation were observed in the lung in all groups including control (no clear dose response). However, because there was no mortality noted in control or low-dose animals, dosing injury was unlikely the only reason for mortality and a relation to test article could not be ruled out. Tooth and hair discoloration was noted at all doses. Mean body weight was lower in mid-dose (-6%) and high-dose males (-9%) at the end of treatment. There were no significant treatment-related effects on ophthalmology, hematology, clinical chemistry, urinalysis, or thyroid analysis parameters (TSH, free T4, and total T4).

Test article-related macroscopic findings (noted at all dose levels) included brown to black discoloration of the thyroid gland, yellow to brown discoloration of the bone and teeth, mild tan discoloration of the liver, and brown foci in the lung. Findings in the liver and lung were not seen after the recovery period. Test article-related histopathological findings included papillary necrosis in the kidney (noted at the mid dose and high dose), centrilobular hepatocellular vacuolation (noted in males at all doses, not associated with cellular necrosis, not associated with liver enzyme increase, greatly reduced after the

recovery period), pigment accumulation in the thyroid gland (noted at all dose levels, not associated with cytotoxicity, not associated with thyroid hormone changes, reduced after the recovery period), and vacuolation in the mesenteric lymph node, small intestine, and gut-associated lymphoid tissue (GALT) (noted at all dose levels, not associated with cellular necrosis, reduced after the recovery period).

The NOAEL was identified as the low dose, 50 mg/kg/day, based on mortality and renal papillary necrosis noted at the mid dose and high dose. See Table 10 for TK results.

Study 4 P005672-HCl: A 39-week oral toxicity study in naive monkeys with a 13-week recovery period (Study# 1753-020)

Oral (gavage) doses of 0 (vehicle), 50, 150, and 400 mg/kg/day sarecycline were administered to cynomolgus monkeys (4/sex/group) once daily for 39 weeks, followed by a 13-week recovery period (2/sex/group for control, mid-dose and high-dose groups). No test article-related mortality was noted. No significant treatment-related effects were noted on body weight, ophthalmology, ECG, hematology, urinalysis, or thyroid analysis parameters (TSH, free T4, and total T4). Increases in liver enzymes (GGT, up to 46%; AST, up to 35%; and ALT, up to 222%) were noted at the high dose in both sexes at the end of treatment. Such findings were no longer noted after the recovery period. Test article-related macroscopic findings (noted at all dose levels) included brown discoloration of the thyroid gland and yellow discoloration of the bone.

Test article-related microscopic findings included minimal centrilobular hepatocellular vacuolation (noted at the mid dose and high dose, reduced after the recovery period), minimal liver focal necrosis (noted in two mid-dose females and one high-dose female), vacuolation in the mesenteric lymph node and small intestine (noted at all dose levels, not associated with cellular necrosis, reduced after the recovery period), minimal to mild pigment accumulation in the thyroid gland (noted at mid dose and high dose, not associated with cytotoxicity, not associated with thyroid hormone change), and minimal bilateral acute inflammation of the renal papillae (noted in 1 high-dose female). Later additional pathology information was provided to help identify the NOAEL. The morphologic appearance and severity of the liver focal necrosis observed in this study was consistent with background findings reported in control cynomolgus monkeys. In addition, this histopathology finding was not seen in males and there was no clear dose-response in females.

Considering that the liver findings at the high dose were associated with increases in liver enzymes, the NOAEL was identified as the mid dose, 150 mg/kg/day. See Table 10 for TK results.

5.5.2. Genetic Toxicology

Study 5 P005672: Bacterial reverse mutation assay (Study# AC20DE.503.BTL)

Sarecycline was tested at doses up to 50 µg/plate, in bacteria strains of *S. typhimurium* TA98, TA100, TA1535, and TA1537, and *E. coli* WP2 uvrA, with and without S9. Significant toxicity was observed at 5 µg/plate and above. This is expected because sarecycline is an antibiotic. There were no significant increases in revertant colonies at any dose, with or without S9. The study was valid. The test result was negative. However, it should be noted that the Ames test has limitations in testing antibiotics.

Study 6 P005672: In vitro mammalian chromosomal aberration test (Study# AC20DE.331.BTL)

Sarecycline was tested at concentrations up to 750 µg/ml for 4 hours of treatment with and without S9 and up to 125 µg/ml for 20 hours of treatment without S9 in CHO cells. Adequate cytotoxicity (at least 50% cell growth inhibition or mitotic inhibition) was achieved in this study. The percentage of cells with structural or numerical aberrations in the test article-treated groups was not significantly increased at any dose level, with or without S9. The study was valid. The result was negative.

Study 7 P005672: In vitro mammalian cell gene mutation test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay) (Study# AC20DE.704.BTL)

Sarecycline was tested at concentrations up to 100 µg/ml for 4 hours of treatment without S9, up to 20 µg/ml for 4 hours of treatment with S9, and up to 25 µg/ml for 24 hours of treatment without S9, in L5178Y/TK$^{+/-}$ mouse lymphoma cells. Adequate cytotoxicity (≤20% relative total growth) was achieved in this study. Sarecycline did not induce significant mutant frequency increase at any dose, with or without S9. The study was valid. The result was negative.

Study 8 Rat bone marrow erythrocyte micronucleus test following oral administration of P005672 (Study# AC20DE.125.BTL)

Single oral (gavage) doses of 0 (vehicle), 100, 300, and 2000 mg/kg sarecycline were administered to SD rats (5/sex/group). Mortality was noted at 2000 mg/kg and additional animals from the replacement group were used. No significant reduction in the ratio of polychromatic erythrocytes to total erythrocytes in dose groups relative to control was observed, suggesting that the test article did not significantly inhibit erythropoiesis. No significant increase in the incidence of micronucleated polychromatic erythrocytes in dose groups relative to control was observed in male or female rats at 24 or 48 hours postdose. The study was valid. The result was negative.

5.5.3. Carcinogenicity

Study 9 P005672-HCl: A 104-week oral carcinogenicity study in mice (Study# 1753-022)

In a 2-year oral (gavage) mouse carcinogenicity study, doses of 0 (vehicle), 10, 30, and 100 mg/kg sarecycline were administered to CD-1 male mice and doses of 0 (vehicle), 10, 30, and 60 mg/kg/day sarecycline were administered to CD-1 female mice. There was no treatment-related effect on mortality. Sarecycline-related macroscopic findings were noted in the thyroid gland, teeth, and bone (discoloration of these organs noted at high dose).

A complete list of tissues was examined histopathologically for all animals. Test article-related microscopic findings were noted in the thyroid gland of males and females at all dose levels and in the kidney of high-dose males. In the thyroid gland, minimal to mild brown to black cytoplasmic pigment accumulation was noted in the follicular epithelial cells in both males and females at all doses. It was not considered adverse as there was no associated cytotoxicity. In the kidney, an increased incidence of papillary necrosis was noted in males at high dose.

There were no significant test article-related neoplastic findings in either sex per the statistical criteria used by the Executive Carcinogenicity Assessment Committee (CAC). See Table 10 for TK results.

Study 10 P005672-HCl: A 104-week oral carcinogenicity study in rats (Study# 1753-021)

In a 2-year oral (gavage) rat carcinogenicity study, doses of 0 (vehicle), 20, 60, and 200/100 mg/kg/day sarecycline were administered to both male and female SD rats. Due to declining survival, the high dose was reduced from 200 mg/kg/day to 100 mg/kg/day during the study for both sexes. All main study animals were terminated early. The dose reduction and early termination received concurrence from the Executive CAC. The increase in mortality in males was dose-related. Test article-related macroscopic observations were noted in the bone, thyroid gland, and teeth. Yellow discoloration of the femur and black or brown discoloration of the thyroid gland were noted in all dose groups of both sexes. Brown discoloration of the teeth was noted at the mid dose and high dose in both sexes.

A complete list of tissues was examined histopathologically for all animals. Test article-related microscopic findings were noted in the kidney, liver, urinary bladder, thyroid gland, mesenteric lymph node, small intestine, and lung. The findings included: papillary edema and necrosis in the kidney in high-dose males and females; centrilobular and diffuse cytoplasmic vacuolation in the liver in high-dose males; a slight increase in transitional cell hyperplasia in the urinary bladder in high-dose males and females; minimal to moderate pigment accumulation in the thyroid gland in all dose groups of both sexes (with no associated cytotoxicity); vacuolation and dilated

lymphatics in the mesenteric lymph node and small intestine in both sexes at mid and high doses (with no associated cytotoxicity); and alveolar bronchiolization in the lung in both sexes at high dose.

There were no significant test article-related neoplastic findings in either sex per the statistical criteria used by the Executive CAC. See Table 10 for TK results.

Note: The two carcinogenicity studies have been reviewed by the Executive CAC. The Committee concurred that both studies were adequate (noting prior approval of the study protocols) and there were no drug-related neoplasms in either study. See Section 13.3.2 for a detailed review of the two studies.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study 11 P005672-HCl: An oral study of fertility and early embryonic development to implantation in rats (Study# 1753-018)

Oral (gavage) doses of 0 (vehicle), 50, 150 and 400 mg/kg/day sarecycline were administered to both male and female SD rats (25/group). For Part A of the study, treated males were mated with untreated females. Dosing began 28 days prior to pairing for the treated males and continued through the mating and postmating period. For Part B of the study, treated females were mated with untreated males. Dosing began 14 days prior to pairing for the treated females and continued through the mating period to gestation Day (GD) 7.

One high-dose male was found dead on Day 50 and a treatment-related effect could not be ruled out. There were no significant treatment-related effects on body weight or food consumption. There were no treatment-related effects on estrous cycle, reproductive or fertility indices, mating performance, or copulatory intervals. There were no significant treatment-related effects on the pregnancy rate or uterine parameters evaluated for either the untreated females mated to treated males or the treated females mated to untreated males. The evaluated parameters included corpora lutea, implantation sites, preimplantation loss, viable embryos, postimplantation loss, litter size, and resorptions.

In sperm evaluation, decreased sperm motility, decreased sperm count and concentration, and an increase in percent abnormal sperm were observed at high dose. A decrease in the organ weight of cauda epididymis was noted at high dose. All the treated males successfully impregnated the corresponding females, with the exception of one high-dose male.

The NOAEL for male fertility was identified as the mid dose, 150 mg/kg/day, based on adverse effects on sperm parameters noted at high dose. The NOAEL for female fertility was identified as the high dose, 400 mg/kg/day. TK analysis was not conducted in this study.

Embryofetal Development

Study 12 P005672-HCl: An oral study for effects on embryofetal development in rats with a toxicokinetic evaluation (Study# 1753-012)

Oral (gavage) doses of 0 (vehicle), 50, 150 and 500 mg/kg/day sarecycline were administered to female SD rats (25/group) from GD 6 to GD 17. Necropsy was conducted on GD 20.

No mortality was noted. All females were found to be pregnant. A decrease in maternal body weight was noted at the high dose. A decrease in fetal body weight and litter size was noted at high dose. An increase in the number of resorption and postimplantation loss was noted at the high dose. Significant skeletal malformations (bent forelimb, hindlimb, and scapula) were observed in all dose groups in a dose-related manner. Forelimb and scapula malformations were present in every litter at the high dose.

Sarecycline was clearly teratogenic in rats under the study conditions. The NOAEL for maternal toxicity was 150 mg/kg/day, while a NOAEL for embryofetal toxicity could not be established in this study. See Table 10 for TK results.

Study 13 P005672-HCl: An oral study for effects on embryofetal development in rabbits with a toxicokinetic evaluation (Study# 1753-013)

Oral (gavage) doses of 0 (vehicle), 50, 100, and 150 mg/kg/day sarecycline were administered to female New Zealand White rabbits (23/group) from GD 7 to GD 19. Necropsy was scheduled on GD 29. Mortality/moribundity/abortion were noted at high dose (10 animals). The remaining 13 high-dose animals were terminated early (GD 25 to GD 27). Two mid-dose females were euthanized early due to moribundity.

Significant body weight loss and decrease in food consumption was noted in maternal animals at high dose. On GD 29, 17, 19, and 15 females in the control, low-dose, and mid-dose groups, respectively, had viable litters for evaluation. High-dose animals were euthanized early with no litter available for evaluation. The uterine examinations did not reveal any test article-related findings at the low dose or mid dose. The parameters evaluated included corpora lutea, implantation sites, preimplantation loss, viable fetuses, postimplantation loss, litter size, and resorptions (early, late, and combined).

No significant effects on fetal sex ratio or mean fetal body weight were noted at the low dose or mid dose. There were no significant test article-related visceral or skeletal malformations noted at low dose or mid dose. The NOAEL for maternal toxicity was identified as 50 mg/kg/day. The NOAEL for embryofetal toxicity was identified as 100 mg/kg/day, under the study conditions. See Table 10 for TK results.

Prenatal and Postnatal Development

Study 14 P005672-HCl: An oral study to evaluate the toxic effects on pre- and postnatal development, including maternal function in rats (Study# 1753-024)

Key Study Findings

- Excessive litter toxicity was noted at high dose, which led to early termination of high-dose F0 dams.
- The NOAEL for maternal toxicity was identified as the low dose, 50 mg/kg/day, based on decreases in body weight and food consumption noted at mid dose during the lactation period.
- The NOAEL for developmental toxicity was identified as the low dose, 50 mg/kg/day, based on decreases noted at mid dose in pup survival, pup weight during the preweaning and growth period, and implantation sites and viable embryos (in F1 females).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 50, 150, and 400 mg/kg/day
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5 M sodium phosphate in deionized water, pH adjusted to 8 ± 0.1
Species/Strain:	Crl:CD®(SD) rats
Number/Sex/Group:	F0 dams: 25 females/group F1 offspring: 25/sex/group
Satellite groups:	None
Study design:	F0 dams were dosed during the period of organogenesis through lactation [from GD 6 to lactation Day (LD) 20]. F1 animals were potentially exposed to the test article in utero and through lactation but were not dosed directly. F0 dams were necropsied on LD 21 (weaning). F1 animals were either necropsied or selected for next generation on postnatal Day (PND) 28. When the selected F1 animals were at least 80 days of age, males and females of the same treatment group were placed together at a 1:1 ratio for mating. The maximum pairing period was 20 days. All females with no confirmed mating date that appeared to be nonpregnant were necropsied 13 days after the last scheduled pairing day. Pregnant F1 females were necropsied on GD 13. F1 males were necropsied after completion of the cesarean section examination.

Deviation from study protocol affecting interpretation of results: None.

Observations and Results

F0 Dams:

There was no test article-related mortality. Due to excessive litter toxicity, the high-dose females were terminated early at parturition. On GD 20, a decrease in mean body weight (-6.6%) was noted at the high dose, compared to control. During lactation, a decrease in mean body weight was noted at the mid dose on LD 4 (-7.4%) and LD 7 (-4.6%), compared to control. During gestation, a decrease in mean food consumption (-11.4%) was noted at the high dose during GD 6 to GD 10, compared to control. During lactation, decreases in mean food consumption were observed at the mid dose (up to -38.1%), compared to control. There were no body weight or food consumption data for high-dose animals during lactation due to early termination.

F1 Litters:

F0 Parturition:
At the high dose, one female was found to be nonpregnant and 21 of 25 animals delivered litters. The animals were terminated at parturition due to excessive litter toxicity (litter loss and stillbirth). Seventy-six percent of the F0 females had total litter loss and 91% of the animals had at least 1 stillborn pup. An increase in gestation length (22.7 versus 21.9 days in controls), and decreases in total pups born (7.0 vs. 11.4 in controls), live pups born per litter (0.5 versus 11.3 in controls), and gestation index (20.8% versus 100% in controls) were noted. This resulted in significant increases in the number of stillborn pups per litter (6.5 versus 0.1 in controls) and stillborn index (87.7% versus 0.7% in controls). However, the total number of implantations per litter was comparable to controls. At the mid dose, all females were pregnant and 24 of 25 animals delivered litters. There were 18 litters (75%) with at least one stillborn pup; however, there was no total litter loss. This resulted in a significant decrease in liveborn pups per litter (7.8 versus 11.3 in controls), and a significant increase in stillborn pups per litter (3.1 versus 0.1 in controls), as well as an increased stillborn index (25.5% versus 0.7% in controls). Gestation length, total pups born per litter, gestation index, and total implantation scars per litter were not significantly different from controls. At the low dose, all females were pregnant and delivered litters. There were no significant findings at the low dose.

F1 Pup Survival:
F1 pup survival over LD 0 to LD 4 pre-cull (viability index) and LD 4 to LD 21 post-cull (lactation index) was evaluated. All litters at the high dose were terminated at parturition, which resulted in a viability index of 0%. At the mid dose, there was a significant decrease in viability index (56% versus 98% in controls); however, the lactation index was comparable to controls (92% versus 99% in controls). Despite the

decreased survival, there were sufficient pups available to proceed with the next generation evaluations. No significant changes in F1 pup survival were noted at the low dose.

F1 sex ratio, clinical observations, and body weight:
There was no significant effect on F1 sex ratio at low dose or mid dose. Clinical observations at the mid dose included decreased activity (10 of 161 pups affected), impaired limb function in the fore and hind limbs (up to 50 of 161 pups affected), skin cold to touch (16 of 161 pups affected), as well as difficult and slow breathing (up to 5 of 161 pups affected). No significant clinical findings were noted at the low dose. Pup weights were recorded on PNDs 0, 4, 7, 14, 21, and 28. Decreases in mean pup weight were noted at the mid dose (up to -28.8%) compared to controls. No significant effect on mean pup weight was noted at the low dose.

F1 Behavioral, Sensory, and Developmental Indices:
F1 pup reflex, sensory, and developmental indices were recorded during the lactation period. No significant effects were noted at the low dose or mid dose. There were no significant changes in sexual maturation parameters, motor activity, or learning or memory assessment at the low dose or mid dose.

F1 In-life Examinations (selected pups):
There were no significant findings in mortality or clinical observations at the low dose or mid dose during the growth phase (Weeks 1 to 13 in males and Weeks 1 to 11 in females). Decreases in mean body weight were noted in mid-dose males during the premating (-18.9%), pairing and postmating periods (-9.1%), and in mid-dose females during the premating period (-18.5%). No significant effect on mean body weight during these periods was noted at the low dose.

F1 Reproductive Performance and Uterine Examination (selected pups):
The reproductive and fertility parameters (including mating, fertility, and fecundity indices, and copulatory intervals) were evaluated and no significant changes were noted at the low dose or mid dose. For uterine examination, at the mid dose, a decrease in the number of implantations per dam (14.0 versus 15.8 in controls) and viable embryos per litter (13.1 versus 15.2 in controls) were observed. No significant changes were noted in the remaining parameters evaluated (corpora lutea, preimplantation loss, postimplantation loss, and resorptions). There were no significant findings noted at low dose.

5.5.5. Other Toxicology Studies

Impurity Safety Evaluation

In the proposed drug substance specifications (refer to the CMC review), the specifications of 6 impurities were set above the ICH Q3A(R2) qualification threshold, which are shown below:

(b) (4)

A computational toxicology assessment was performed for these impurities using 2 quantitative structure activity relationship (QSAR) analyses, Derek Nexus and Leadscope Model Applier. Overall, there were no significant concerns for genotoxicity or carcinogenicity potential for these impurities. All impurities were present in the lots used in either the subchronic or chronic oral toxicity studies or the 2-year oral carcinogenicity studies. Overall, the toxicology data support the proposed specifications for these impurities.

Phototoxicity Evaluation

The phototoxic potential of sarecycline was evaluated in female SKH1-*hr* hairless mice. Intravenous doses up to 75 mg/kg/day sarecycline were administered once daily for 2 days, followed by UVA radiation at 4.8 mW/cm^2 for 1 hour after each dose. Skin reaction was observed daily for 4 days using a grading system that included measures of erythema, edema, flaking, and scabbing. Sarecycline showed dose-related phototoxicity mainly at doses ≥50 mg/kg.

In a second phototoxicity study in female SKH1-*hr* hairless mice, single intracutaneous doses up to 0.375 mg/mice sarecycline were administered, followed by UVA radiation at 5 mW/cm^2 for 1 hour. Skin reaction was observed for 3 days. Sarecycline showed skin reactions (erythema, edema, flaking, and scab) indicating phototoxicity at the 0.375 mg dose.

Juvenile Animal Toxicity Evaluation

No juvenile animal toxicology studies were conducted with sarecycline. The applicant initially submitted a pediatric study plan to IND 107645, proposing to study sarecycline in pediatric subjects 12 years of age and older. In the chronic toxicology studies (6-month rat study and 9-month monkey study), the animal ages at the initiation of the 2 studies were approximately equivalent to the adolescent phase in humans. Therefore, the proposed age group was supported by nonclinical data. Subsequently the sponsor proposed to change the pediatric age group to be studied to 9 years of age and older. Considering that the noted toxicity profile of sarecycline (liver and renal toxicities) in the chronic toxicology studies was consistent with the class effects of tetracyclines, and was not expected to differ significantly in the age range of 9 to 12 years, the proposed age group is still acceptable from a pharmacology/toxicology perspective. No juvenile animal toxicology study is needed to support the proposed pediatric population.

5.5.6. Multiples of Human Exposure Calculation

The multiples of human exposure based on AUC comparison between the NOAELs identified in pivotal toxicology studies and the proposed maximum recommended human dose (MRHD; 150 mg/day) are shown in Table 11 below.

Table 11: Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	AUC (µg·hr/ml)	Multiples of human exposure[d] (based on AUC comparison)
26-week rat study	Oral	50	250	5.2
39-week monkey study	Oral	150	174	3.6
2-year carcinogenicity study in mice	Oral	Male: 100[a]	56.7	1.2
		Female: 60[a]	45.2	0.9
2-year carcinogenicity study in rats	Oral	200/100[a]	363	7.5
Fertility and early embryonic development study in rats	Oral	Male: 150	193[b]	4.0
		Female: 400	379[b]	7.9
Embryofetal development study in rats	Oral	Maternal: 150	122	2.5
		Embryofetal: None	None	None
Embryofetal development study in rabbits	Oral	Maternal: 50	27.2	0.6
		Embryofetal: 100	31.3	0.6
Pre- and postnatal development study in rats	Oral	Maternal: 50	69.4[c]	1.4
		Developmental: 50	69.4[c]	1.4

[a]Dose level of no neoplastic findings for carcinogenicity studies
[b]AUC values (Day 1) from the 26-week rat study
[c]AUC value (GD 17) from the embryofetal development study in rats
[d]Compared with the human AUC value at the maximum recommended human dose (MRHD; 150 mg/day): 48.2 µg·hr/ml (Day 7 value, from clinical trial SRC-PK-06)

6 Clinical Pharmacology

6.1. Executive Summary

Sarecycline is a novel tetracycline-class antibiotic.

- Applicant's proposed indication: (b) (4)
- Applicant's proposed dosing regimen: (b) (4) once daily with or without food, with the dose administered based on the body weight range as shown in the table below:

(b) (4)

The Applicant evaluated SEYSARA with the proposed dosing regimen shown in the above table in two phase 3 trials and a long-term extension study using the to-be marketed formulation. Prior to phase 3, the Applicant conducted a phase 2 dose-ranging trial to support dose selection for phase 3 trials, which forms the basis for dose response evaluations. The Applicant additionally submitted the results of phase 1 trials conducted in healthy subjects, subjects with impaired renal function, and subjects with impaired hepatic function to support the PK assessment of sarecycline.

The key review questions focus on the appropriateness of the proposed sarecycline dosing regimen (b) (4) and recommendations for the sarecycline dose in patients with hepatic or renal impairment.

SEYSARA was administered as 60 mg, 100 mg, or 150 mg tablets (body weight-based dose range of 1.1 to 1.8 mg/kg) once daily in subjects who weighed 33 to 54 kg, 55 to 84 kg, and 85 to 136 kg, respectively, in the phase 3 trials. (b) (4)

Based on the study results, dose adjustment is not proposed in subjects with mild to moderate hepatic impairment and in subjects with mild to severe renal impairment.

Therefore, the dosing regimen recommended for approval is once daily, with or without food, with the dose based on the body weight ranges as shown in the table below:

Body Weight (kg)	Tablet Strength
33 to 54 kg	60 mg tablet
55 to 84 kg	100 mg tablet
85 to 136 kg	150 mg tablet

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable to support the approval of sarecycline tablets for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

The key review findings with specific recommendations/comments are summarized below in Table 12.

Table 12: Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of sarecycline for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris was established in two Phase 3 trials (SC1401 and SC1402).
General dosing instructions	The proposed dosing regimen of 60 mg for patients who weigh 33-54 kg, 100 mg for patients who weigh 55-84 kg, and 150 mg for patients who weigh 85-136 kg, once daily with or without food, is acceptable. (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. • No dose adjustment is recommended for patients with mild to severe renal impairment. No data are available in patients with end stage renal disease.
Labeling	The review team has specific content and formatting change recommendations. See "Labeling Recommendations" in Section 6.2.2. of this review.
Bridge between the to-be-marketed and clinical trial Formulations	• The to-be-marketed formulation was used in Phase 3 trials.
Drug-drug interactions	• For P-glycoprotein (P-gp) substrates, the potential for a clinically relevant drug interaction cannot be ruled out and hence monitoring of subjects who are on concomitant medications that are P-gp substrates and have narrow therapeutic index is recommended. • Results from the clinical drug-drug interaction study (SRC-PK-08) with oral hormonal contraceptives in healthy female subjects suggested that the potential of a clinically relevant effect of sarecycline on the efficacy of oral contraceptives containing ethinyl estradiol and norethindrone acetate is low. • In vitro study results suggest that the potential for a clinically relevant drug interaction is low for compounds metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5.

6.1.2. Post-Marketing Requirement(s) and Commitment(s)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1 Mechanism of Action

The mechanism of action of sarecycline in treating acne vulgaris is not known.

6.2.1.2 Clinical Pharmacokinetics

Absorption: Following once daily oral administration of sarecycline tablets 60 mg, 100 mg, or 150 mg in healthy subjects, the median time to peak plasma concentration (T_{max}) of sarecycline was observed at 1.5 to 2.0 hours post-dose; steady-state exposure of sarecycline was reached by Day 7; observed maximum plasma concentration (C_{max}) and area under the plasma concentrations versus time profile (AUC) values increased slightly less than proportionally with increasing dose (60 mg, 100 mg, and 150 mg) at steady-state. A mean accumulation ratio of sarecycline ranging from 1.5 to 1.6 was observed.

Co-administration of a single dose of sarecycline 150 mg in healthy subjects with a high-fat, high-calorie meal that included milk resulted in a delay in T_{max} by approximately 0.53 hour (approximately 32 minutes) and a decrease in sarecycline C_{max} and AUC by 31% and 27%, respectively, when compared to administration of sarecycline under fasting conditions. No dose adjustments are recommended.

Distribution: An in vitro study demonstrated that sarecycline was 62.5% to 74.7% bound to human plasma proteins at tested sarecycline concentrations of 0.5 µg/mL to 50 µg/mL. The mean apparent volume of distribution of sarecycline at steady-state ranged from 91.4 L to 97.0 L.

Elimination: In healthy subjects, following once daily oral administration, the mean apparent oral clearance (CL/F) of sarecycline at steady state was 2.97 L/h to 3.22 L/h; the mean elimination half-life was 21 to 22 hours.

Metabolism: In vitro studies using human liver microsomes suggested minimal metabolism (<15%). Sarecycline (the 4S-epimer) undergoes non-enzymic epimerization into R-sarecycline, the 4R-epimer, in vivo. R-sarecycline is not pharmacologically active and the systemic exposure to R-sarecycline at steady-state represents <10% relative to that of sarecycline (the 4S-epimer).

Excretion: After a single oral dose of radiolabeled sarecycline 100 mg, the average recovery of the dose was 42.6% in feces (14.9% as unchanged) and 44.1% in urine (24.7% as unchanged).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is (b) (4) dosed orally as 60 mg, 100 mg, or 150 mg in patients who weigh 33-54 kg, 55-84 kg, or 85-136 kg, respectively, once daily with or without food. The phase 3 studies SC1401 and SC1402 evaluated sarecycline at the proposed doses (i.e., either 60 mg, 100 mg, or 150 mg tablets, once daily, in subjects who weighed 33 to 54 kg, 55 to 84 kg, and 85 to 136 kg, respectively) in patients with moderate to severe acne vulgaris. The proposed doses were effective in treating inflammatory lesions of acne and appeared to have an acceptable safety profile.

(b) (4)

In conclusion, the dosing regimen of 60 mg, 100 mg, or 150 mg in patients who weigh 33-54 kg, 55-84 kg, or 85-136 kg, respectively, once daily with or without food is acceptable.

Therapeutic Individualization

Specific Populations

Patients with Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In a dedicated hepatic impairment study, mild (Child-Pugh A; n=8) or moderate (Child-Pugh B; n=8) hepatic impairment had no clinically relevant effect on the systemic exposure of sarecycline. When compared to healthy subjects with normal hepatic function (n=8), mean sarecycline C_{max} and AUC values were decreased by approximately 12% and 14%, respectively, in subjects with mild hepatic impairment. The decreases were not deemed clinically relevant. Subjects with moderate hepatic impairment had similar sarecycline systemic exposures (C_{max} and AUC) compared to healthy subjects with normal hepatic function.

Patients with Renal Impairment: No dose adjustment is recommended in patients with mild to severe renal impairment. In a dedicated renal impairment study conducted in healthy subjects with normal renal function [estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2; n=8], and in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=8), moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=8), or severe (eGFR 15 to 29 mL/min/1.73 m^2; n=8) renal impairment, renal impairment had no clinically relevant effect on the systemic exposure of sarecycline. No dose adjustment is recommended.

Drug-Drug Interactions

Oral Contraceptives: In a dedicated drug-interaction study conducted in healthy female subjects (n=26), the effect of sarecycline on the PK of norethindrone and ethinyl estradiol was evaluated. When the oral contraceptive was co-administered with multiple daily doses of 150 mg sarecycline tablet, norethindrone $C_{max,ss}$ and $AUC_{0\text{-}tau,ss}$ was 18% and 23% higher and ethinyl estradiol $C_{max,ss}$ and $AUC_{0\text{-}tau,ss}$ was 14% and 11% higher, respectively, compared to those when the oral contraceptive was administered alone. The results indicated that co-administration with sarecycline is not expected to produce a clinically significant effect on the efficacy of oral contraceptives containing norethindrone acetate 1 mg and ethinyl estradiol 20 mcg.

P-gp Substrates: Sarecycline inhibited P-gp with an inhibitory concentration 50% (IC_{50}) value of 6.95 µM when digoxin was used as a P-gp substrate in an in vitro transporter assay. In a drug interaction study conducted in healthy subjects, co-administration of a single dose of 150 mg sarecycline tablet caused a 26% increase in digoxin $C_{max,ss}$ while $AUC_{0\text{-}tau,ss}$ did not change compared to that when digoxin was dosed alone. These study results should be interpreted with caution because of the following limitations of the study design: (1) the available data did not adequately assess the effect of sarecycline on the elimination of digoxin because the plasma and urine samples for measurement of digoxin were collected during the time (i.e., 24 hours post dose) that was less than one half-life of digoxin (i.e., 1.5 to 2.0 days); and (2) a single dose of sarecycline was used while the proposed dosing regimen of sarecycline is once daily administration, and sarecycline has a mean accumulation ratio of 1.5 to 1.6. Based on the observation of a 26% increase in digoxin $C_{max,ss}$ caused by a single dose of sarecycline 150 mg, the interaction potential between sarecycline and P-gp substrates dosed orally cannot be ruled out. Thus, it is recommended that safety be monitored for digoxin and other P-gp substrates that have a narrow therapeutic index and may require dosage adjustment when given concurrently with sarecycline.

6.3. Outstanding Issues

None.

6.4. Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling recommendation and comments:

(Decisions on the labeling language regarding interaction potential with oral retinoids, penicillin, and anticoagulants were based upon clinical team's recommendation.)

Section 2 Dosage and Administration: Remove the language (b) (4)

Section 7 Drug Interactions: Rearrange the content into two subsections depending on whether the potential of the effect is imposed or received by SEYSARA. Remove the

(b) (4) Add information for P-gp substrates. Simplify the information regarding the oral hormonal contraceptives.

Section 12.2 Pharmacodynamics: Add this subsection. Provide the information on cardiac electrophysiology.

Section 12.3 Pharmacokinetics: Rearrange format of content to be consistent with the current clinical pharmacology labeling guidance. Add results of food effect, distribution, elimination, and drug interaction studies. Removed (b) (4) and replace with a brief description of these results and the impact of other covariates (i.e., age, weight, and sex).

6.5. Comprehensive Clinical Pharmacology Review

6.5.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	The mechanism of action for sarecycline in treating acne vulgaris is unknown.
QT prolongation	No QTc prolongation to any clinically relevant extent.
General Information	
Bioanalysis	Sarecycline and a minor metabolite, R-sarecycline, were measured using validated LC/MS/MS methods. A summary of the method validation reports is included in appendix.
Drug exposure at steady state following the therapeutic dosing regimen	In a crossover study SRC-PK-06 conducted in 24 healthy subjects with median (range) body weight of 74.3 (56-98) kg, following 7-day once daily administration of 60 mg, 100 mg, and 150 mg sarecycline tablets, the mean (% CV) C_{max} of sarecycline was 1590 (22%) ng/mL, 2620 (25%) ng/mL, and 3820 (32%) ng/mL, respectively; the mean (%CV) $AUC_{0\text{-}tau}$ was 20700 (15%) ng*h/mL, 33800 (17%) ng*h/mL, and 48200 (19%) ng*h/mL, respectively.
Dose proportionality	Steady-state exposure increased in a slightly less-than-proportional manner within the doses of 60 mg, 100 mg, and 150 mg administered once daily.
Accumulation	The mean accumulation ratio of sarecycline ranged from 1.5- to 1.6-fold at steady state (day 7) with repeated once daily dosing.
Absorption	
Oral bioavailability	Absolute oral bioavailability has not been determined. At the highest proposed dose of 150 mg, an oral solution formulation indicated bioequivalence to the to-be-marketed formulation (i.e., oral tablet) in healthy subjects.
Bioequivalent (BE) between tablets and capsules	BE between 100 mg tablets and 100 mg capsules at a single dose of 100 mg. The tablets(test)/capsules (reference) geometric mean ratio (GMR) [90% confidence interval (CI)] were within the no effect boundary of 80% to 125% as shown below: C_{max}:100.67% (97.23%, 104.23%) $AUC_{0\text{-}last}$: 99.76% (97.01%, 102.59%) $AUC_{0\text{-}inf}$: 99.57% (96.63%, 102.60%)
T_{max} (hours)	Median values ranged from 1.5 to 2.0 hours post-dose at steady state
Food effect (FDA recommended high-fat breakfast*)	At a single dose of 150 mg sarecycline tablet, the values of fed/fasted GMR (90% CI) are:

	C_{max}: 68.69% (62.55%, 75.44%) $AUC_{0\text{-}last}$: 73.29% (67.04%, 80.13%) $AUC_{0\text{-}inf}$: 73.81% (67.48%, 80.74%)
Distribution	
Volume of distribution	Following multiple once daily administration of sarecycline at doses of 60 mg, 100 mg, and 150 mg in healthy subjects, the apparent volume of distribution (Vz/F) at steady-state ranged from 91 L to 97 L.
Plasma protein binding	Mean in vitro protein binding of sarecycline in human plasma ranged from 62.5% to 74.7%.
Substrate of transporter systems	Sarecycline is not a substrate for P-gp, BCRP, OATP1B1, or OATP1B3.
Elimination	
Half-life	Following 7 days of once-daily oral dosing of sarecycline at 60 mg, 100 mg, or 150 mg in healthy subjects, the mean plasma half-life of sarecycline was 21-22 hours.
Clearance	The mean apparent oral clearance (CL/F) of sarecycline at steady-state approximately is 3 L/h.
Metabolism	
Primary metabolic pathway(s)	Metabolism of sarecycline by enzymes in human liver microsomes is minimal (< 15%) in vitro. R-sarecycline, a product resulting from non-enzymic epimerization, was the most abundant circulating metabolite in plasma. The mean C_{max} of R-sarecycline was 3% relative to the C_{max} of sarecycline. Other minor metabolites resulting from O-/N-demethylation, hydroxylation, and desaturation have been found in human plasma, urine, and feces samples.
Inhibitor/Inducer	Sarecycline is a P-gp inhibitor with an IC_{50} value of 6.95 µM for the P-gp mediated transport of digoxin. Sarecycline does not inhibit OATP1B1, OATP1B3, OCT2, OAT1, OAT3, or BCRP. Sarecycline is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 with IC_{50} values greater than 100 µM. Sarecycline is not likely an inducer for CYP1A2, CYP2B6, or CYP3A4/5 at concentrations up to 15 µM, which is approximately 3-fold of the C_{max} at steady state following the therapeutic dosing regimen.
Excretion	
Primary excretion pathways	In an oral mass balance trial, the mean (SD) radioactivity recovery of the administered dose in feces and urine was 42.6 (5.2)% and 44.1 (4.6)%, respectively.

*FDA high-fat (approximately 50% of total caloric content of the meal), high calorie (800-1000 calories) breakfast contained two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces (100 g) of hash brown potatoes, and eight fluid ounces (240 mL) of whole milk.

6.5.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The pivotal evidence of effectiveness comes from the efficacy results in a phase 2 dose-ranging study, PR-10411, and two pivotal phase 3 trials, SC1401 and SC1402. Exploratory exposure-response (ER) analyses for efficacy were conducted using model-predicted individual steady state sarecycline exposure (AUC_{ss}) and efficacy data from phase 2 and 3 trials, which suggests a positive correlation between steady state sarecycline exposure and 1 of the 2 coprimary endpoints, change in inflammatory lesion counts from baseline, although the ER relationship is relatively flat.

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

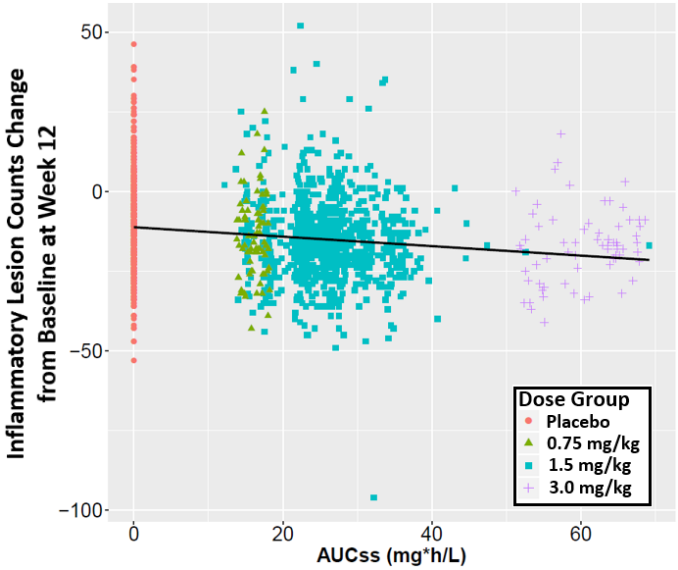
Yes. The proposed doses of 60 mg, 100 mg, or 150 mg for patients who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively, once daily with or without food, are effective and appear to have acceptable safety profiles. The majority of the treatment-emergent adverse events were assessed as mild to moderate in severity. Nausea was the only TEAE that occurred with a ≥1% higher incidence in the sarecycline group compared with the placebo group (3.1% versus 2.0%, respectively). Refer to Section 7 for more details.

(b) (4)

Furthermore, the proposed doses of sarecycline were demonstrated to be effective and had acceptable safety in the phase 3 trials. Therefore, the Applicant's proposed dosing regimen (i.e., 60 mg, 100 mg, or 150 mg once daily for patients who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively) is appropriate.

ER Relationship for Efficacy:
The relationship between population PK model-predicted individual steady state sarecycline exposure (AUC_{ss}) and the observed change of inflammatory lesion counts from baseline in phase 2 and phase 3 trials is shown in Figure 1.

Figure 1: Relationship of Change in Inflammatory Lesion Counts from Baseline at Week 12 and AUC_{ss} of Sarecycline in Patients with Moderate to Severe Facial Acne Vulgaris



Source: Reviewer's plot based on data provided by the Applicant. The black line is a linear regression line.

A correlation was found but the ER relationship is relatively flat. The placebo group had an observed mean (SD) change in inflammatory lesion counts from baseline of -10.8 (12.6) while the dose groups of approximately 0.75 mg/kg (actual range: 0.57 to 0.96 mg/kg), 1.5 mg/kg (actual range: 0.82 to 1.92 mg/kg), and 3 mg/kg (actual range: 2.3 to 3.8 mg/kg) had mean (SD) changes in inflammatory lesion counts from baseline of -14.4 (13), -15.6 (12.4), and -17.1 (11.7), respectively. There was no significant relationship between sarecycline exposure and treatment success using the IGA score.

ER relationship for Safety:
The ER relationship for safety in the proposed target patient population is not characterized.

QT Prolongation:
Sarecycline was not associated with prolongation of the corrected QT interval (QTc) in healthy subjects at a single dose of 500 mg.

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

No dose adjustments are needed for mild to moderate hepatic impairment, mild to severe renal impairment, or other intrinsic factors such as sex or age.

Hepatic Impairment:
A dedicated hepatic impairment study, SRC-PK-03, was conducted in patients with mild (Child-Pugh Class A, n=8) or moderate (Child-Pugh Class B, n=8) hepatic impairment,

and in healthy subjects (n=8) with normal hepatic function. A single oral dose of 150 mg sarecycline tablet was administered approximately 2 hours after a light breakfast.

The summary of sarecycline PK parameters and statistical comparison (pair-wise comparison of Child-Pugh A and B to healthy subjects) are described inTable 13Table 13Table 13Table 13Table 13Table 13 Table 13. In patients with mild hepatic impairment (Child-Pugh A), there was a 14% decrease in sarecycline total exposure, and in patients with moderately impaired hepatic function (Child-Pugh B) there was a 7% increase in sarecycline total exposure, compared to subjects with normal hepatic function. The observed effects of mild or moderate hepatic impairment on sarecycline exposure were not clinically meaningful. Dose adjustments for patients with mildly to moderately impaired hepatic function (Child-Pugh A to B) are not recommended for sarecycline.

Table 13: Summary of Sarecycline PK Parameters in Hepatic Impairment Study

Hepatic Impairment Levels	C_{max} (ng/mL)		$AUC_{0\text{-}inf}$ (ng•h/mL)	
	Arithmetic Mean (CV %)	GMR (90% CI)	Arithmetic Mean (CV %)	GMR (90% CI)
Healthy (Normal)	2730 (34)	-	48,400 (26)	-
Child-Pugh A (Mild)	2360 (41)	88.12 (67.84, 114.45)	40,400 (25)	86.46 (71.44, 104.63)
Child-Pugh B (Moderate)	2270 (36)	99.20 (75.33, 130.65)	45,700 (24)	106.72 (87.30, 130.45)

Source: Table 11-1 and Table 11-2 in study report.

Renal Impairment: A dedicated renal impairment study, SRC-PK-04, was conducted in patients with mild, moderate, or severe renal impairment (n=8/group) and in healthy subjects (n=8) with normal renal function. A single oral dose of 150 mg sarecycline tablet was administered approximately 2 hours after a light breakfast.

The summary of sarecycline PK parameters and statistical comparison (pair-wise comparison of patients with renal impairments to healthy subjects) are described in Table 14. There were 14% and 17% increases in sarecycline total exposure in patients with moderate and severe renal impairment, respectively, compared to patients with normal renal function. The increase in sarecycline exposure caused by impaired renal function was not clinically meaningful. No dose adjustment is recommended in patients with mild to severe renal impairment.

Table 14: Summary of Sarecycline PK Parameters in Renal Impairment Study

Renal Impairment Levels	C_{max} (ng/mL)		AUC_{0-inf} (ng•h/mL)	
	Arithmetic Mean (CV %)	GMR (90% CI)	Arithmetic Mean (CV %)	GMR (90% CI)
Healthy (Normal)	2530 (26)	-	44,800 (16)	-
Mild Renal Impairment	2440 (22)	96.88 (77.28, 121.45)	43,000 (10)	96.72 (84.58, 110.60)
Moderate Renal Impairment	1850 (17)	73.92 (58.97, 92.67)	50,800 (14)	113.76 (99.48, 130.09)
Severe Renal Impairment	2140 (33)	82.82 (66.07, 103.83)	52,800 (22)	116.81 (102.15,133.58)

Source: Table 11-1 and Table 11-2 in study report.

Sex and Age: Based on a population PK analysis, females are predicted to have approximately 15.6% higher AUC at steady state compared to males. This difference is not considered clinically meaningful. Age was not an influential covariate on the PK parameters of sarecycline.

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

Yes. Sarecycline is a P-gp inhibitor. Patients on P-gp substrates with a narrow therapeutic index that may require dosage reductions should be monitored for adverse reactions. The potential for a clinically relevant effect of sarecycline on the efficacy of oral hormonal contraceptives containing ethinyl estradiol and norethindrone acetate is expected to be low. No clinically relevant food effect was observed with sarecycline.

Effect of Sarecycline on P-gp Substrates

An open label, 2-treatment, fixed-sequence study, SRC-PK-07, was conducted to assess the effects of sarecycline on the PK of digoxin, a P-gp substrate. All subjects received oral administration of one 0.25 mg digoxin tablet once daily on Days 1 to 10 followed by co-administration of one 0.25 mg digoxin tablet and one 150 mg sarecycline tablet on Day 11. Intensive blood PK samples and urine PK samples were collected predose and during a period of 24 hours postdose administration on Day 10 (10^{th} dose of digoxin alone) and on Day 11 (co-administration of digoxin and sarecycline). Digoxin $C_{max,ss}$ was increased by approximately 26% while $AUC_{0-tau,ss}$ did not change when concomitantly administered with sarecycline (Table 15).

Table 15: Summary of Digoxin PK Parameters with or without Concomitant Administration of Sarecycline.

Parameter	Units	Geometric Mean by Treatment		Test:Reference Ratio (%)	90% Confidence Interval
		Digoxin and Sarecycline (Treatment B, Test)	Digoxin Alone (Treatment A, Reference)		
$C_{max,ss}$	ng/mL	2.20	1.74	126.04	114.30 to 138.98
$AUC_{0-\tau,ss}$	ng·h/mL	17.5	17.0	103.20	100.26 to 106.22
$T_{max,ss}$[a]	h	0.67 (0.67 to 2.00)	1.00 (0.67 to 2.00)		
$Ae_{0-\tau,ss}$	mg	0.130	0.145		
$CL_{R,ss}$	mL/min	123	142		

Treatment A = Test = multiple-dose oral administration of Lanoxin (digoxin tablet, 0.25 mg) alone (Day 10)
Treatment B = Reference = multiple-dose oral administration of Lanoxin (digoxin tablet, 0.25 mg) coadministered with a single sarecycline tablet, 150 mg (Day 11)
$C_{max,ss}$ = Maximum plasma concentration at steady-state
$AUC_{0-\tau,ss}$ = Area under the plasma concentration versus time curve from time 0 to τ, at steady-state
$T_{max,ss}$ = Time of maximum concentration at steady-state
$Ae_{0-\tau,ss}$ = The cumulative amount of unchanged drug excreted into the urine during the dosing interval, τ, at steady-state
$CL_{R,ss}$ = Renal clearance at steady-state calculated as $Ae_{0-\tau,ss}/AUC_{0-\tau,ss}$
[a] The median (range) is presented

Source: Table 11-1 in study report.

Decreases (10% to 13%) in renal clearance and cumulative amount of drug excreted into the urine were also observed. Caution should be given for the interpretation of the study results for the following reasons: (1) sarecycline will be administered once daily in patients while a single dose of sarecycline was administered in this digoxin interaction study; and (2) the plasma and urine samples for measurement of digoxin were collected during the time (i.e., 24 hours post dose) that was less than one half-life of digoxin (i.e., 1.5 to 2.0 days according to the approved labelling of Lanoxin®). Therefore, a clinically relevant interaction potential between sarecycline and P-gp substrates cannot be ruled out because the effect on the elimination phase could not be adequately determined based on the data obtained from the study. Thus, safety should be monitored for digoxin and other P-gp substrates that may require dosage reductions when co-administered with sarecycline.

Effect of Sarecycline on Oral Hormonal Contraceptives

An open label fixed-sequence study, SRC-PK-08, was conducted to assess the effect of sarecycline tablets on the PK of norethindrone and ethinyl estradiol following multiple-dose oral administration of norethindrone acetate/ethinyl estradiol tablets in healthy female subjects. All subjects received 1 norethindrone acetate (1 mg)/ethinyl estradiol tablet (20 mcg) per day from Days 1 to 14 (Treatment A) followed by once daily co-administration of 1 norethindrone acetate/ethinyl estradiol tablet with one 150 mg sarecycline tablet from Days 15 to 24 (Treatment B). Steady state exposure of norethindrone and ethinyl estradiol was reached within the first treatment period (Days 1-14) when norethindrone acetate/ethinyl estradiol tablets were administered alone. Steady-state exposure of norethindrone, ethinyl estradiol, and sarecycline was also

reached within the second treatment period (Days 15 to 24) when norethindrone acetate/ethinyl estradiol tablets were co-administered with sarecycline tablets.

Co-administration of a single dose of sarecycline did not change the systemic exposure ($C_{max,ss}$ and $AUC_{0\text{-}tau,ss}$) of norethindrone and ethinyl estradiol (Day 15 versus Day 14). Co-administration of multiple dose sarecycline caused an increase in the $C_{max,ss}$ and $AUC_{0\text{-}tau,ss}$ of norethindrone by 18% and 23% (Table 16), and an increase in the $C_{max.ss}$ and $AUC_{0\text{-}tau,ss}$ of ethinyl estradiol by 14% and 11% (Table 17), respectively (Day 24 versus Day 14). The increased exposure of norethindrone and ethinyl estradiol is not considered clinically relevant. The results suggested that the potential for a clinically relevant effect of sarecycline on the efficacy of oral contraceptives containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol is low.

Table 16: Summary of Norethindrone PK Parameters with or without Concomitant Administration of Sarecycline

Parameter	Units	Geometric Mean by Treatment		Test: Reference Ratio (%)	90% Confidence Interval
		Day 15 (Treatment B - Test)	Day 14 (Treatment A - Reference)		
$C_{max,ss}$	pg/mL	12841.78	12457.35	103.09	94.56 to 112.39
$AUC_{0\text{-}\tau,ss}$	pg·h/mL	87626.19	83513.50	104.92	101.00 to 109.00
		Day 24 (Treatment B - Test)	Day 14 (Treatment A - Reference)		
$C_{max,ss}$	pg/mL	14649.20	12457.35	117.59	107.86 to 128.20
$AUC_{0\text{-}\tau,ss}$	pg·h/mL	102472.75	83513.50	122.70	118.11 to 127.47

Day 14 / Treatment A = Following multiple-dose daily administration of NA/EE tablets alone

Day 15 / Treatment B = Following multiple-dose daily administration of NA/EE tablets coadministered with a single sarecycline tablet

Day 24 / Treatment B = Following multiple-dose daily administration of NA/EE tablets coadministered with daily sarecycline tablets

Source: Table 11-2 in study report.

Table 17: Summary of Ethinyl Estradiol PK Parameters With or Without Concomitant Administration of Sarecycline

Parameter	Units	Geometric Mean by Treatment		Test: Reference Ratio (%)	90% Confidence Interval
		Day 15 (Treatment B - Test)	Day 14 (Treatment A - Reference)		
$C_{max,ss}$	pg/mL	67.08	62.31	107.65	102.21 to 113.38
$AUC_{0-\tau,ss}$	pg·h/mL	588.01	583.21	100.82	97.13 to 104.67
		Day 24 (Treatment B - Test)	Day 14 (Treatment A - Reference)		
$C_{max,ss}$	pg/mL	70.80	62.31	113.63	107.89 to 119.68
$AUC_{0-\tau,ss}$	pg·h/mL	648.22	583.21	111.15	107.06 to 115.39

Day 14 / Treatment A = Following multiple-dose daily administration of NA/EE tablets alone
Day 15 / Treatment B = Following multiple-dose daily administration of NA/EE tablets coadministered with a single sarecycline tablet
Day 24 / Treatment B = Following multiple-dose daily administration of NA/EE tablets coadministered with daily sarecycline tablets

Source: Table 11-4 in study report.

Food Effect on the PK of Sarecycline

The food effect on the PK of sarecycline in the to-be-marketed formulation at the proposed highest strength (150 mg tablet) was evaluated in an open-label, randomized, 3-treatment, 3-period, 6-sequence crossover study (Study PR-11914). Healthy subjects were randomly assigned to one of 6 treatment sequences of 3 treatments (a single 150 mg sarecycline tablet under fasting conditions; a single 150 mg sarecycline tablet after a high-fat meal; and an aqueous solution containing 150 mg sarecycline, fasted), with treatment periods separated by 9 days. The results indicated that co-administration with a high-fat (approximately 50% of total caloric content of a meal), high-calorie (800 to 1000 calories) meal that included milk delayed sarecycline T_{max} by approximately 0.53 hour and decreased C_{max} by 31% and AUC by 27% (Table 18). The observed difference in the sarecycline exposure between fed and fasted conditions was not considered clinically relevant.

Table 18: Summary of Sarecycline PK Parameters Following a Single Dose of 150 mg Tablets, With or Without Food in Healthy Subjects (n=20)

Analyte	Parameter	Geometric mean or [Median (Range)]		Ratio (%) (Test:Reference)	90% Confidence Interval
		Sarecycline tablet, 150 mg with food (Test)	Sarecycline tablet, 150 mg fasted (Reference)		
Sarecycline	C_{max}	1700	2480	68.69	62.55 to 75.44
	AUC_{0-t}	30200	41400	73.29	67.04 to 80.13
	$AUC_{0-\infty}$	31800	43200	73.81	67.48 to 80.74
	T_{max}	[2.53 (1.00 to 6.00)]	[2.00 (1.00 to 4.00)]	NC	NC

Source: Table 11-3 in study report.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Sarecycline was evaluated in 14 phase 1 clinical studies (in healthy subjects and in patients with impaired hepatic or renal function), as well as a phase 2 dose-ranging study, 2 pivotal phase 3 clinical trials, and a long-term extension safety study in patients with moderate to severe acne vulgaris.

The primary evidence that supports the use of sarecycline for the target indication is based on data from 4 studies (see Table 19):

- A dose-ranging, supportive phase 2 study (Study PR-10411) that evaluated sarecycline capsules at approximately 0.75, 1.5, and 3.0 mg/kg compared with placebo capsules administered orally once daily for 12 weeks in 284 patients (modified intent-to-treat [mITT] population) 12 to 43 years of age with moderate to severe acne vulgaris.

- Two multicenter, randomized, double-blind, placebo-controlled, pivotal phase 3 studies that compared sarecycline tablets (60 mg, 100 mg, and 150 mg) and placebo tablets administered orally once daily for 12 weeks in a total of 2002 patients (ITT population) 9 to 45 years of age with moderate to severe acne vulgaris (Studies SC1401 and SC1402).

- A phase 3 long-term extension study (Study SC1403) of the 2 pivotal phase 3 studies that evaluated a total of 483 subjects (safety population) 9 to 44 years of age with moderate to severe acne vulgaris who were exposed to sarecycline 60 mg, 100 mg or 150 mg orally once daily for up to an additional 40 weeks; this included 247 patients previously exposed to sarecycline in Study SC1401 or SC1402 and an additional 236 patients who received placebo in Study SC1401 or SC1402.

Table 19: Pertinent Clinical Studies Included in the Clinical Development Program for Sarecycline

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients (enrolled/ completed)	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety						
SC1401	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Sarecycline 60 mg, 100 mg, 150 mg daily as tablets vs. placebo/ 1:1 ratio of 2 treatment groups	Administered orally once daily for 12 weeks	968/825	10 to 45 years Safety: 964	56 sites in the U.S.
SC1402	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Sarecycline 60 mg, 100 mg, 150 mg daily as tablets vs. placebo/ 1:1 ratio of 2 treatment groups	Administered orally once daily for 12 weeks	1034/877	9 to 44 years Safety: 1026	54 sites in the U.S.
SC1403	Multicenter, open-label study	Sarecycline 60 mg, 100 mg, 150 mg daily as tablets	Administered orally once daily for 40 weeks	483/354	9 to 44 years Safety: 483	52 sites in the U.S.
Studies to Support Safety						
PR-10411	Multicenter, randomized, double-blind, placebo-controlled study	Sarecycline 0.75, 1.5, or 3.0 mg/kg/day as capsules vs placebo/ 1:1:1:1 ratio of 4 treatment groups	Administered orally once daily for 12 weeks	285/245	12 to 43 years Safety: 285	38 sites in the U.S.
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
PR-01010	Single-center, randomized, double-	Sarecycline 20, 40, 80, 160, 240,	Single oral dose	64/64	20 to 45 years	1 site in the U.S.

(PK)	blind, placebo-controlled, single ascending-dose study	320, 400, or 480 mg as capsules vs placebo				
PR-07112 (through QT)	Single-center, randomized, double-blind, placebo- and moxifloxacin-controlled, double-dummy, single-dose, 3-treatment, 3-period, 6-sequence, crossover study	Sarecycline 500 mg as capsules vs moxifloxicine 400 mg capsule vs placebo/ 1:1:1:1:1:1 ratio of 6 treatment sequences	Single oral dose	48/41	18 to 45 years	1 site in the U.S.

Supportive safety data are provided from 14 clinical studies that assessed the bioavailability, pharmacodynamics, phototoxicity, PK, safety, and tolerability of sarecycline. These clinical studies were conducted with sarecycline at doses ranging from 20 to 500 mg within a capsule, tablet, or oral solution formulation, and specifically included 14 phase 1 studies that enrolled 382 healthy subjects. One of the phase 1 studies (Study SRC-PK-04) also enrolled 24 patients with impaired renal function, and another (Study SRC-PK-03) enrolled 16 patients with impaired hepatic function.

7.1.2. Clinical Data

Data Sources

The sources of data used for the evaluation of the efficacy and safety of sarecycline for the proposed indication included final study reports submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)], and literature references.

This application was submitted in eCTD format and hence was entirely electronic. The electronic submission including protocols, SAPs, clinical study reports, SAS transport datasets in legacy, SDTM, and ADaM format are in the following network path:

- Original submission: \\CDSESUB1\evsprod\NDA209521\209521.enx

Data and Analysis Quality

No issues with the data quality.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The Applicant conducted two identically-designed, randomized, multicenter, double-blind, placebo-controlled, 12-week, phase 3 trials (Studies SC1401 and SC1402) to evaluate the efficacy and safety of sarecycline compared to placebo for the treatment of non-nodular inflammatory lesions of acne vulgaris. For enrollment, the protocols specified the following key inclusion criteria:

- Male or female, 9 to 45 years of age, inclusive
- Body weight between 33 kg and 136 kg, inclusive
- Has facial acne vulgaris with:
  - 20 to 50 inflammatory lesions (papules, pustules, and nodules)
  - Up to 100 non-inflammatory lesions (open and closed comedones)
  - No more than two nodules on the face
  - An IGA score of moderate (3) or severe (4): see Table 20 for details on the IGA.

Table 20: Investigator Global Assessment of Inflammatory Acne

Score	Grade	Description
0	Clear	No evidence of papules or pustules
1	Almost Clear	Rare inflammatory papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Few inflammatory lesions (papules/pustules only; no nodulocytic lesions)
3	Moderate	Multiple inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocytic lesions
4*	Severe	Inflammatory lesions are more apparent, many papules/pustules; there may or may not be a few nodulocytic lesions

Source: protocols for Studies SC1401 and SC1402
*Acne that worsens beyond Grade 4 will be recorded as an adverse event on the CRF

Each trial was designed to enroll and randomize approximately 1000 subjects in a 1:1 ratio to either sarecycline tablet (N=500) or placebo tablet (N=500). The dose of sarecycline was based on weight, see Table 21. Subjects took the oral tablet once daily for 12 weeks. The protocols specified evaluating subjects at screening, baseline (Week 0), and Weeks 3, 6, 9, and 12.

Table 21: Sarecycline Dose Selection

Body Weight	Tablet Strength	Total Dose per Weight Mass
33 to 54 kg	60 mg tablet	1.8 to 1.1 mg/kg
55 to 84 kg	100 mg tablet	1.8 to 1.2 mg/kg
85 to 136 kg	150 mg tablet	1.8 to 1.1 mg/kg

The protocols specified the following co-primary efficacy endpoints:

- Absolute change from baseline in inflammatory lesion counts at Week 12
- The proportion of subjects with success on IGA at Week 12, where success is defined as at least a 2-point decrease from baseline and a score of 0 (clear) or 1 (almost clear).

The protocols specified the following secondary efficacy endpoints:

- Percent change from baseline in inflammatory lesion counts at Week 12
- Absolute and percent change from baseline in inflammatory lesion counts at Week 9
- Absolute and percent change from baseline in inflammatory lesion counts at Week 6
- Absolute and percent change from baseline in inflammatory lesion counts at Week 3

After the Pre-NDA meeting, the Applicant submitted the finalized SAPs for their phase 3 trials (Study SC1402 on February 13, 2017, and Study SC1401 on February 28, 2017). The Applicant submitted an amended SAP for Study SC1401 on March 6, 2017, which added absolute and percent change from baseline in non-inflammatory lesion as secondary efficacy endpoints. It should be noted that the Applicant amended the SAP after unblinding and analyzing the data from Study SC1402. The amended SAP for Study SC1401 lists the following secondary endpoints:

- Percent change from baseline in inflammatory lesion counts at Week 12
- Absolute and percent change from baseline in inflammatory lesion counts at Week 9
- Absolute and percent change from baseline in inflammatory lesion counts at Week 6
- Absolute and percent change from baseline in inflammatory lesion counts at Week 3
- Absolute and percent change from baseline in non-inflammatory lesion counts at Week 12
- Absolute and percent change from baseline in non-inflammatory lesion counts at Week 9
- Absolute and percent change from baseline in non-inflammatory lesion counts at Week 6
- Absolute and percent change from baseline in non-inflammatory lesion counts at Week 3

7.2.2. Statistical Methodologies

The protocol-specified primary analysis population is the ITT population, defined as all randomized subjects. The protocol also specified conducting supportive analyses using the Per-Protocol (PP) population, defined as all randomized subjects, excluding subjects who:

- Did not meet inclusion/exclusion criteria
- Had taken any interfering concomitant medications
- Duration of treatment was less than 68 days or overall study drug compliance less than 80%
- Received treatment different from the assigned treatment

For the analysis of the co-primary efficacy endpoint of absolute change from baseline in inflammatory lesion counts at Week 12, the protocol specified using analysis of covariance (ANCOVA) with treatment, analysis (pooled) center, and baseline lesion counts as covariates in the model. The protocol specified that the interaction between baseline lesion counts and treatment would be included in the model if the p-value for the interaction was ≤0.05. Furthermore, the protocol specified that a treatment-by-center (pooled) interaction would be investigated as an exploratory analysis to assess the homogeneity of treatment effects across analysis (pooled) centers. If the interaction is significant at the $p<0.10$ level, the protocol specified producing interaction plots to determine the nature of the interaction and to identify any "outlier" centers, and any such centers may be further investigated for explanation involving study conduct, subject demographics, current medications, etc. If large differences in treatment effects are seen in any "extreme" centers, the protocol specified conducting sensitivity analyses that exclude centers with the highest extreme treatment effect values from the analysis.

For the analysis of the co-primary efficacy endpoint of success on IGA (i.e., at least 2-grade improvement from baseline AND a score of 0 or 1) at Week 12, the protocol specified using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis (pooled) center. The protocol specified using the Breslow-Day test to investigate the homogeneity of treatment effects across analysis (pooled) centers. The protocol specified that if the Breslow-Day test indicated large heterogeneity in the odds ratios across analysis (pooled) centers, then "further exploration may be done graphically or with further investigation for explanation involving study conduct, subject demographics, current medications, etc."

The protocol-specified primary method for handling missing data is the multiple imputation (MI) approach. The protocol specified that missing data for each treatment arm would be imputed separately using the model approach, which includes age, sex, and the measurements of the endpoint at each visit (baseline, and Weeks 3, 6, 9, and 12). Missing data will be imputed 20 times.

For the co-primary endpoint of absolute change from baseline in inflammatory lesion counts at Week 12, the protocol specified the following sensitivity analyses for the handling of missing data:

- Impute missing data using the baseline observation carried forward (BOCF) approach.
- Impute missing data using the last observation carried forward (LOCF) approach.
- Analyze this endpoint using the mixed model repeated measures (MMRM) approach with treatment, analysis (pooled) center, visit, baseline lesion count, and the interaction between treatment and visit in the model. An unstructured covariance matrix will be initially specified for the correlation; however, if the model does not converge, the Toeplitz covariance structure will be used.

For the co-primary endpoint of success on IGA, the protocol specified the following sensitivity analyses for the handling of missing data:

- Impute missing data as failures (i.e., non-responders)
- Impute missing data using the worst-case scenario (i.e., missing data for subjects on sarecycline will be imputed as failures and missing data for subjects on placebo will be imputed as successes)

7.2.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Study SC1401 enrolled and randomized a total of 968 subjects (483 to sarecycline and 485 to placebo) from 56 centers in the United States. Study SC1402 enrolled and randomized a total of 1034 subjects (519 to sarecycline and 515 to placebo) from 54 centers in the United States. Table 22 presents the disposition of subjects for Studies SC1401 and SC1402. The discontinuation rates were generally similar between the treatment arms within each trial and between each trial.

Table 22: Disposition of Subjects for Studies SC1401 and SC1402 [ITT(1)]

	Study SC1401		Study SC1402	
	Sarecycline (N=483)	**Placebo (N=485)**	**Sarecycline (N=519)**	**Placebo (N=515)**
Discontinued	63 (13%)	80 (16%)	86 (17%)	71 (14%)
Adverse Event	3 (<1%)	7 (1%)	11 (2%)	6 (1%)
Lack of Efficacy	0	1 (<1%)	1 (<1%)	3 (<1%)
Lost to Follow-Up	21 (4%)	34 (7%)	39 (8%)	36 (7%)
Non-Compliance with Study Drug	7 (1%)	2 (<1%)	4 (1%)	3 (<1%)
Other	2 (<1%)	3 (<1%)	6 (1%)	6 (1%)
Protocol Violation	2 (<1%)	1 (<1%)	0	1 (<1%)
Withdrawal of Consent	28 (6%)	32 (7%)	25 (5%)	16 (3%)

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects.

For both Studies SC1401 and SC1402, Table 23 presents the demographics and Table 24 presents the baseline disease characteristics. The demographics were generally balanced across the treatment arms within each trial and were similar between the two trials. In addition, the baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between the two trials. In both trials, approximately 85% of subjects had a baseline IGA score of 3 (moderate). As noted in Section 7.2.1, subjects were not required to have a minimum number of non-inflammatory lesions at baseline.

Table 23: Demographics for Studies SC1401 and SC1402 [ITT(1)]

	Study SC1401		Study SC1402	
	Sarecycline (N=483)	**Placebo (N=485)**	**Sarecycline (N=519)**	**Placebo (N=515)**
Age (years)				
Mean (SD)	19.6 (6.5)	19.8 (6.9)	20.4 (6.7)	19.7 (6.4)
Median	17.0	18.0	18.0	17.0
Range	10 to 45	10 to 45	9 to 44	10 to 44
Categories				
9-11	4 (1%)	6 (1%)	7 (1%)	4 (1%)
12-17	241 (50%)	235 (49%)	285 (55%)	256 (50%)
18+	238 (49%)	244 (50%)	227 (44%)	255 (49%)
Sex				
Male	215 (45%)	214 (44%)	204 (39%)	223 (43%)
Female	268 (55%)	271 (56%)	315 (61%)	292 (57%)
Race(2)				
American Indian or Alaska Native	2 (<1%)	3 (<1%)	5 (1%)	9 (2%)
Asian	11 (2%)	9 (2%)	23 (4%)	21 (4%)
Black or African American	80 (17%)	79 (16%)	66 (13%)	76 (15%)
Multiple	11 (2%)	14 (3%)	13 (3%)	15 (3%)
Native Hawaiian / Pacific Islander	2 (<1%)	3 (<1%)	4 (1%)	3 (<1%)
White	377 (78%)	377 (78%)	407 (79%)	391 (76%)
Baseline Weight (kg)				
Mean (SD)	71.9 (17.7)	71.2 (17.1)	72.7 (19.1)	71.5 (17.3)
Median	68.8	68.0	68.7	68.0
Range	40.6 to 135.3	40.8 to 135.2	36.5 to 135.6	38.1 to 134.5
Categories				
33 to 54 kg	73 (15%)	73 (15%)	72 (14%)	64 (12%)
55 to 84 kg	306 (63%)	319 (66%)	337 (65%)	354 (69%)
85 to 136 kg	104 (22%)	93 (19%)	110 (21%)	97 (19%)

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects.
(2) One subject in Study SC1402 randomized to sarecycline had missing race information.

Table 24: Baseline Disease Characteristics for Studies SC1401 and SC1402 [ITT(1)]

	Study SC1401		Study SC1402	
	Sarecycline (N=483)	Placebo (N=485)	Sarecycline (N=519)	Placebo (N=515)
IGA Score				
3 – Moderate	413 (86%)	410 (85%)	440 (85%)	439 (85%)
4 – Severe	70 (14%)	75 (15%)	79 (15%)	76 (15%)
Inflammatory Lesions				
Mean (SD)	29.7 (8.7)	30.2 (9.6)	30.3 (8.5)	30.2 (8.7)
Median	27	27	28	28
Range	20 to 64	18 to 89	20 to 56	20 to 59
Non-Inflammatory Lesions				
Mean (SD)	42.4 (21.3)	43.7 (21.1)	42.3 (19.5)	43.9 (20.6)
Median	37	38	39	40
Range	0 to 123	0 to 100	0 to 108	0 to 100
Categories – Minimums				
≥ 10	471 (97%)	475 (98%)	496 (96%)	495 (96%)
≥ 20	436 (90%)	448 (92%)	469 (90%)	464 (90%)
≥ 30	360 (75%)	376 (78%)	414 (80%)	416 (81%)

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects.

7.2.4. Results for the Co-Primary Efficacy Endpoints

Table 25 presents the results of the co-primary efficacy endpoints for both trials in the ITT population. In both trials, sarecycline was statistically superior to placebo for both co-primary efficacy endpoints (p-values ≤0.004). The results for the PP population (not shown) were similar to those for the ITT population.

Table 25: Results of the Co-Primary Efficacy Endpoints at Week 12 for Studies SC1401 and SC1402 [ITT(1)]

	Study SC1401			Study SC1402		
Endpoint	Sarecycline (N=483)	Placebo (N=485)	P-value	Sarecycline (N=519)	Placebo (N=515)	P-value
IGA Success(2,3)	21.9%	10.5%	<0.001	22.6%	15.3%	0.004
Absolute Change (Reduction) in Inflammatory Lesion Counts:						
Mean	15.3	10.2		15.5	11.1	
LS Mean(4)	15.3	10.1	<0.001	15.1	10.7	<0.001

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) Success is defined as an IGA score of 0 or 1 with at least a 2-point decrease from baseline.
(3) P-value is based on a CMH test stratified by analysis (pooled) center.
(4) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

Table 26 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 pre-specified imputation methods. The results were generally similar across the various methods except for IGA success under the worst-case scenario, which had placebo being more efficacious than sarecycline. However, as the placebo response rate for completers was 10.8% in Study SC1401 and 15.2% in Study SC1402, it is not reasonable to assume all subjects that discontinued placebo would have been successes if they did not discontinue.

Table 26: Results for the Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data

	Study SC1401			Study SC1402		
	Sarecycline (N=483)	**Placebo (N=485)**	**P-value**	**Sarecycline (N=519)**	**Placebo (N=515)**	**P-value**
Subjects with Missing Data	*57 (12%)*	*76 (16%)*	--	*78 (15%)*	*67 (13%)*	--
IGA Success[1]						
MI (primary)[2, 7]	21.9%	10.5%	<0.001	22.6%	15.3%	<0.001
Failure[3, 7]	19.7%	8.7%	<0.001	18.7%	13.2%	0.009
Observed	22.5%	10.8%	<0.001	22.7%	15.2%	<0.001
Worst-Case[4, 7]	19.7%	25.2%	0.029	18.7%	27.0%	<0.001
Absolute Change in Inflammatory Lesion Counts:						
MI (primary)[2, 8]	15.3	10.2	<0.001	15.5	11.1	<0.001
BOCF[5, 8]	13.7	8.5	<0.001	13.0	9.8	<0.001
LOCF[6, 8]	14.8	9.9	<0.001	14.9	10.5	<0.001
Observed[9]	15.6	10.1	<0.001	15.3	11.2	<0.001

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Success is defined as an IGA score of 0 or 1 with at least a 2-point decrease from baseline.
(2) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(3) Missing data was imputed as failures (i.e., non-responders).
(4) Missing data for sarecycline is imputed as failures and missing data for placebo is imputed as successes.
(5) Missing data is imputed using the baseline observation carried forward (BOCF).
(6) Missing data is imputed using the last observation carried forward (LOCF).
(7) P-value based on a CMH test stratified by analysis (pooled) center.
(8) P-value based on an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.
(9) P-value based on mixed model repeated measures (MMRM) with fixed effects of treatment, analysis (pooled) center, and visit, the baseline value as the covariates, and the treatment-by-visit interaction term.

7.2.5. Results for the Secondary Efficacy Endpoints Related to Inflammatory Lesion Counts

Table 27 and Table 28 present the results for the secondary efficacy endpoints related to inflammatory lesion counts for Studies SC1401 and SC1402, respectively. In both trials, sarecycline was statistically superior to placebo (p-values <0.001) for both absolute and percent change (reduction) from baseline in inflammatory lesion counts at all post-baseline visits (i.e., Weeks 3, 6, 9, and 12).

Table 27: Results for Absolute and Percent Change (Reduction) in Inflammatory Lesion Counts for Study SC1401 [ITT(1)]

	Absolute Change in Inflammatory Lesion Counts			Percent Change in Inflammatory Lesion Counts		
	Sarecycline (N=483)	Placebo (N=485)	P-value	Sarecycline (N=483)	Placebo (N=485)	P-value
Week 12	*Co-Primary Endpoint*					
Mean	15.3	10.2		52.2	35.2	
LS Mean(2)	15.3	10.1	<0.001	51.8	35.1	<0.001
Week 9						
Mean	13.9	10.2		47.5	35.0	
LS Mean(2)	13.9	10.0	<0.001	47.4	34.9	<0.001
Week 6						
Mean	12.6	8.6		42.6	29.3	
LS Mean(2)	12.5	8.4	<0.001	42.2	28.9	<0.001
Week 3						
Mean	8.5	6.5		29.7	22.5	
LS Mean(2)	8.5	6.4	<0.001	29.6	22.4	<0.001

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

Table 28: Results for Absolute and Percent Change (Reduction) in Inflammatory Lesion Counts for Study SC1402 [ITT(1)]

	Absolute Change in Inflammatory Lesion Counts			Percent Change in Inflammatory Lesion Counts		
	Sarecycline (N=519)	Placebo (N=515)	P-value	Sarecycline (N=519)	Placebo (N=515)	P-value
Week 12	*Co-Primary Endpoint*					
Mean	15.5	11.1		50.8	36.4	
LS Mean(2)	15.1	10.7	<0.001	49.9	35.4	<0.001
Week 9						
Mean	13.7	9.9		45.3	32.9	
LS Mean(2)	13.4	9.5	<0.001	44.5	31.9	<0.001
Week 6						
Mean	12.0	8.3		39.9	28.2	
LS Mean(2)	11.7	8.0	<0.001	39.1	27.3	<0.001
Week 3						
Mean	8.5	5.6		28.3	18.9	
LS Mean(2)	8.4	5.5	<0.001	28.0	18.6	<0.001

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

7.2.6. Results for the Secondary Efficacy Endpoints Related to Non-Inflammatory Lesion Counts

As noted in Section 7.2.1, the Applicant amended the SAP for Study SC1401 by adding absolute and percent change (reduction) from baseline in non-inflammatory lesion counts at Weeks 3, 6, 9, and 12 as secondary efficacy endpoints. It should be noted that this was done after unblinding and analyzing the data from Study SC1402; therefore, these endpoints were not specified as secondary efficacy endpoints in Study SC1402. In addition, it should be noted that the protocols for both trials did not specify a minimum non-inflammatory lesion count as an inclusion criterion for enrollment in the trials.

Table 29 presents the results for absolute and percent change (reduction) in non-inflammatory lesion counts at each post-baseline visit (i.e., Weeks 3, 6, 9, and 12) for Study SC1401. For absolute change, only the p-value for Week 3 was greater than 0.05; however, for percent change, all of the p-values were >0.05. This difference is primarily due to subjects with a small number of baseline non-inflammatory lesions that then increased during the trial. For example, one subject had 1 non-inflammatory lesion at baseline that increased to 34 at Week 12, which is a 3300% increase. Consequently, the Applicant conducted post hoc analyses including only subjects that had ≥10, ≥20, and ≥30 non-inflammatory lesions at baseline.
Table 30 presents the results for absolute and percent change (reduction) in non-inflammatory lesion counts in subjects with ≥20 non-inflammatory lesions at baseline. For absolute change, while the reductions for both sarecycline and placebo increased, the treatment effects were generally similar to those in the overall population (i.e., all subjects). For percent change, the reductions in both groups and the treatment effects were greater compared to the overall population.

Table 31 presents the results for absolute and percent change (reduction) in non-inflammatory lesion counts at each post-baseline visit (i.e., Weeks 3, 6, 9, and 12) in all subjects for Study SC1402. The results for only subjects with ≥20 non-inflammatory lesions at baseline are presented in Table 32. Both sets of results for Study SC1402 were similar to those for Study SC1401; however, as previously noted, absolute and percent change (reduction) in non-inflammatory lesions were not secondary efficacy endpoints and not included in the multiplicity testing strategy for Study SC1402.

Table 29: Results for Absolute and Percent Change (Reduction) in Non-Inflammatory Lesion Counts for Study SC1401 [ITT(1)]

	Absolute Change (Reduction) in Non-Inflammatory Lesion Counts			Percent Change (Reduction) in Non-Inflammatory Lesion Counts		
	Sarecycline (N=483)	Placebo (N=485)	P-value	Sarecycline (N=483)	Placebo (N=485)	P-value
Week 12						
Mean	14.7	11.2		25.1	22.2	
LS Mean(2)	15.1	11.2	0.001	27.0	22.7	0.579
Week 9						
Mean	12.6	9.6		19.2	17.9	
LS Mean(2)	13.0	9.6	0.001	20.8	18.0	0.697
Week 6						
Mean	9.9	8.3		12.1	16.9	
LS Mean(2)	10.6	8.6	0.037	14.6	17.6	0.738
Week 3						
Mean	7.0	6.6		6.0	13.8	
LS Mean(2)	7.9	7.1	0.381	8.0	14.3	0.2861

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

Table 30: Results for Absolute and Percent Change (Reduction) in Non-Inflammatory Lesion Counts in Subjects with ≥20 Non-Inflammatory Lesions at Baseline for Study SC1401 [ITT(1)]

	Absolute Change (Reduction) in Non-Inflammatory Lesion Counts		Percent Change (Reduction) in Non-Inflammatory Lesion Counts	
	Sarecycline (N=436)	Placebo (N=448)	Sarecycline (N=436)	Placebo (N=448)
Week 12				
Mean	16.3	12.3	35.6	27.7
LS Mean(2)	16.4	12.4	35.7	28.0
Week 9				
Mean	14.2	10.7	31.1	24.4
LS Mean(2)	14.3	10.8	31.4	24.8
Week 6				
Mean	11.1	9.1	24.8	20.5
LS Mean(2)	11.7	9.6	26.0	21.7
Week 3				
Mean	8.0	7.3	17.1	15.7
LS Mean(2)	8.9	7.9	18.2	16.7

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

Table 31: Results for Absolute and Percent Change (Reduction) in Non-Inflammatory Lesion Counts for Study SC1402 [ITT(1)]

	Absolute Change (Reduction) in Non-Inflammatory Lesion Counts		Percent Change (Reduction) in Non-Inflammatory Lesion Counts	
	Sarecycline (N=519)	Placebo (N=515)	Sarecycline (N=519)	Placebo (N=515)
Week 12				
Mean	16.6	14.7	28.5	22.5
LS Mean(2)	16.2	13.4	25.7	17.5
Week 9				
Mean	15.4	13.2	23.7	19.7
LS Mean(2)	15.2	12.1	22.7	16.7
Week 6				
Mean	11.9	10.9	18.5	15.1
LS Mean(2)	11.6	10.0	18.9	13.8
Week 3				
Mean	7.7	7.9	7.5	5.6
LS Mean(2)	7.7	7.4	7.5	3.6

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

Table 32: Results for Absolute and Percent Change (Reduction) in Non-Inflammatory Lesion Counts in Subjects with ≥20 Non-Inflammatory Lesions at Baseline for Study SC1402 [ITT(1)]

	Absolute Change (Reduction) in Non-Inflammatory Lesion Counts		Percent Change (Reduction) in Non-Inflammatory Lesion Counts	
	Sarecycline (N=469)	Placebo (N=464)	Sarecycline (N=469)	Placebo (N=464)
Week 12				
Mean	18.2	16.4	38.2	33.4
LS Mean(2)	17.4	14.7	35.2	29.7
Week 9				
Mean	17.0	14.8	35.5	29.7
LS Mean(2)	16.9	13.6	34.0	27.4
Week 6				
Mean	13.3	12.3	28.4	25.5
LS Mean(2)	12.7	11.1	26.3	23.0
Week 3				
Mean	8.6	9.2	18.6	18.6
LS Mean(2)	8.6	8.6	17.3	17.1

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.
(2) LS means and p-values from an ANCOVA model with terms for treatment, analysis (pooled) center, and baseline lesion counts.

7.2.7. Exploratory Analysis: IGA and Non-Inflammatory Lesions

As previously noted, the IGA scale was based on only inflammatory lesions; therefore, an investigator's global assessment of "clear" or "almost clear" for acne vulgaris as a whole (i.e., both inflammatory and non-inflammatory lesions) was not performed in Studies SC1401 and SC1402. The statistical reviewer explored success definitions based on both IGA score and non-inflammatory lesion counts at Week 12 to obtain a general idea of how the product would perform at treating acne vulgaris, see Table 33. The results are based on only subjects with ≥20 non-inflammatory lesions at baseline, which has been used in previous development programs for moderate to severe acne vulgaris as an inclusion criterion for non-inflammatory lesions. The first row presents the response rates based only on IGA success (i.e., an IGA score ≤1), and the second row requires both IGA success and no more than 20 non-inflammatory lesions. In several other acne vulgaris development programs, the description for "almost clear" in an IGA used the term "rare" when describing the number of inflammatory and non-inflammatory lesions. The third and fourth row of Table 33 presents two interpretations of "rare" for the number of non-inflammatory lesions (i.e., ≤10 and ≤5). The response rates decrease as the criterion for non-inflammatory lesions becomes more stringent.

Table 33: Success Definitions Based on IGA (Only Inflammatory Lesions) and Non-Inflammatory Lesion Counts at Week 12 for Studies SC1401 and SC1402

	Study SC1401		Study SC1402	
	Sarecycline	**Placebo**	**Sarecycline**	**Placebo**
Baseline Non-Inflammatory Lesions ≥ 20:	N=436	N=448	N=469	N=464
IGA ≤ 1 at Week 12	19.1%	10.1%	21.6%	15.5%
IGA ≤ 1 & Non-Inflam ≤ 20 at Week 12	11.6%	6.7%	15.1%	10.9%
IGA ≤ 1 & Non-Inflam ≤ 10 at Week 12	8.2%	3.7%	11.0%	5.9%
IGA ≤ 1 & Non-Inflam ≤ 5 at Week 12	5.5%	1.7%	7.1%	2.8%

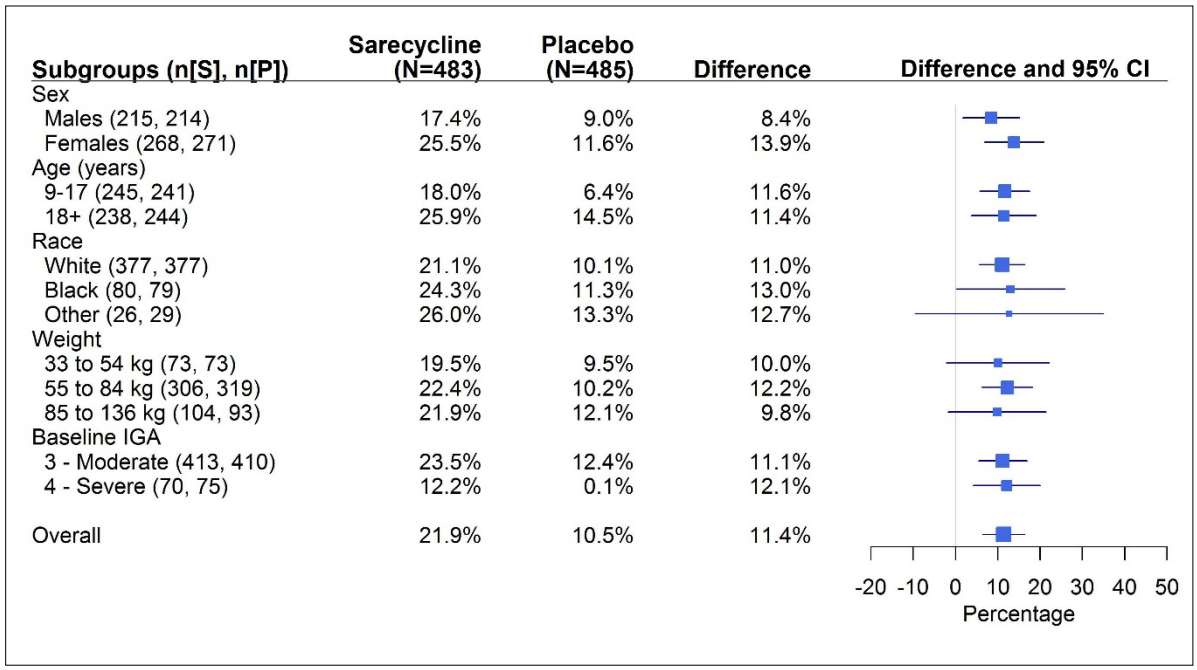
Source: Statistical Reviewer's Analysis
(1) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

7.2.8. Findings in Special/Subgroup Populations

7.2.8.1 Sex, Age, Race, Weight, 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), weight (33 to 54 kg, 66 to 84 kg, and 85 to 136 kg), and baseline IGA score for Studies SC1401 and SC1402 are presented in Figure 2 and Figure 3, respectively. The results for absolute change (reduction) from baseline in inflammatory lesion counts at Week 12 by these same subgroups for Studies SC1401 and SC1402 are presented in Figure 4 and Figure 5, respectively. Treatment effects were generally consistent across the subgroups, with some variability from the smaller subgroups (e.g., race) and placebo response rate (e.g., IGA success for females treated with placebo in Study SC1402). There were no substantial differences in efficacy across the subgroups.

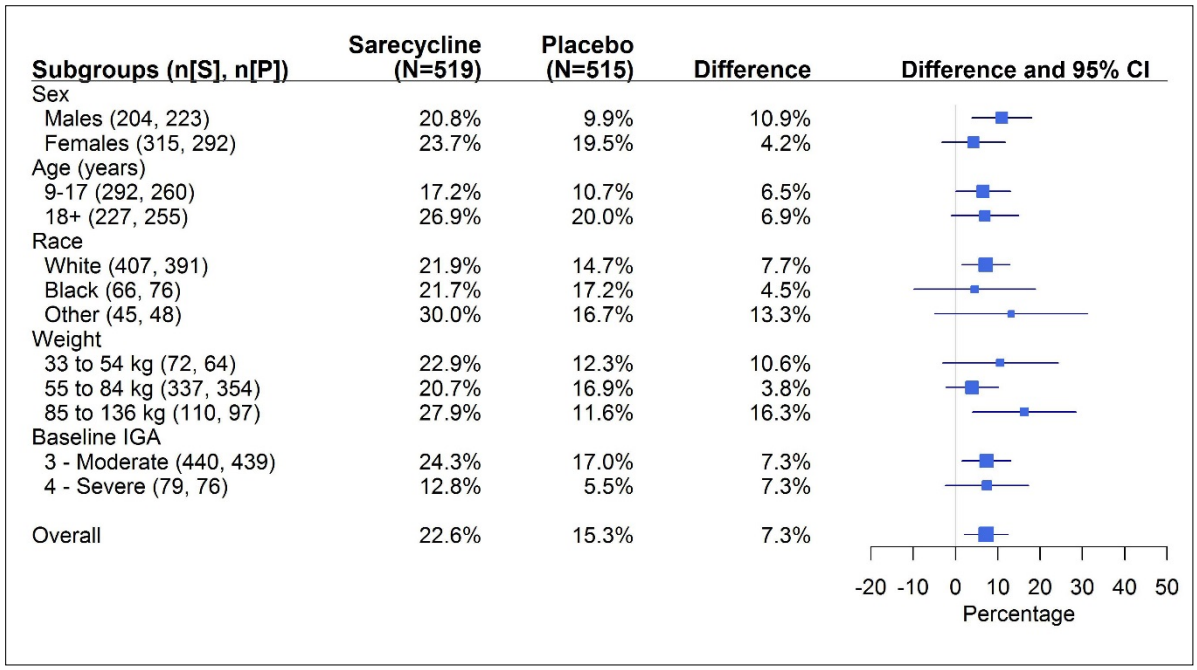
Figure 2: IGA Success at Week 12 by Sex, Age, Race, Weight, and Baseline IGA Score for Study SC1401 [ITT(1)]



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

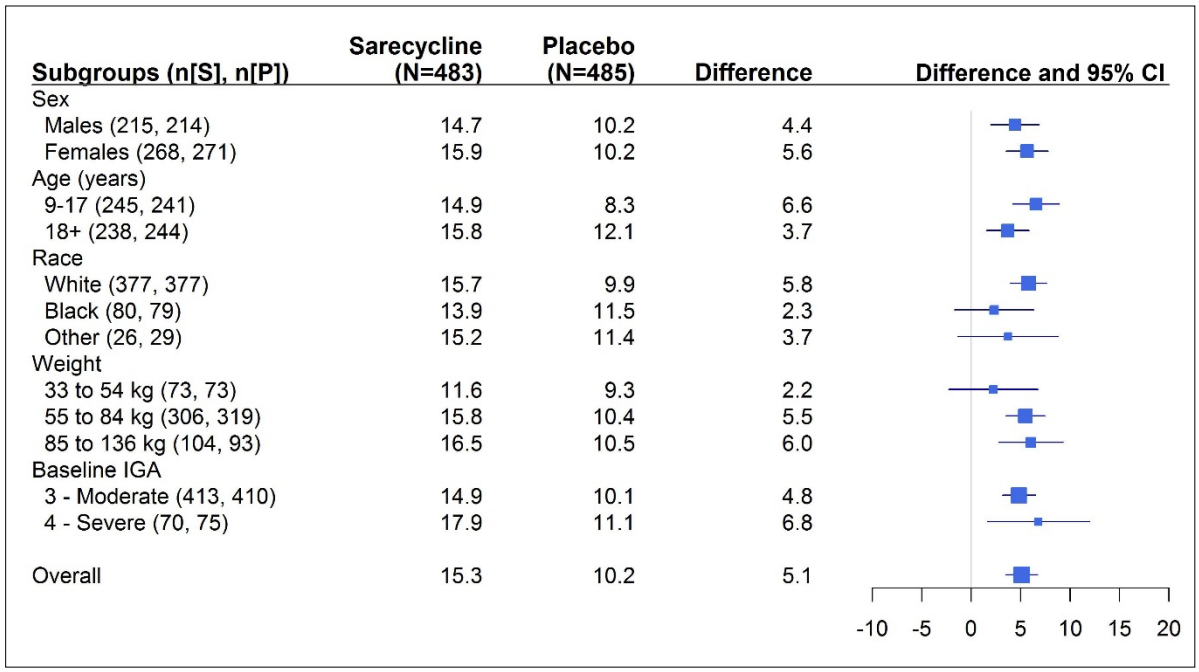
Figure 3: IGA Success at Week 12 by Sex, Age, Race, Weight, and Baseline IGA Score for Study SC1402 [ITT(1)]



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

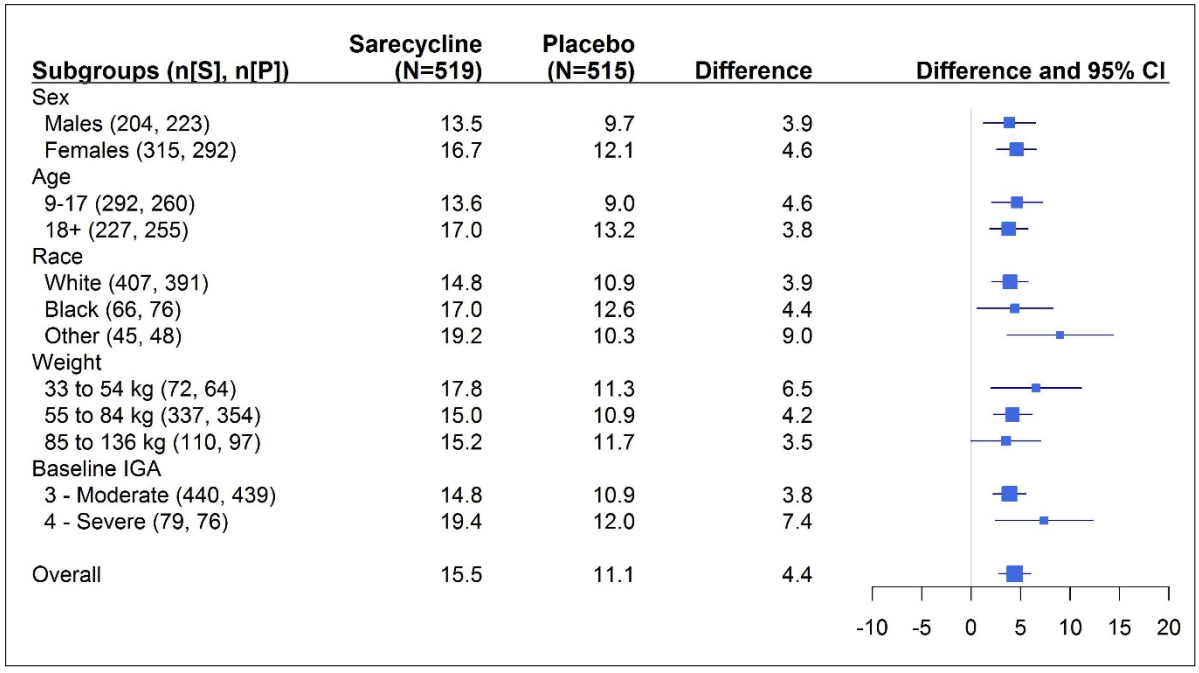
Figure 4: Absolute Change from Baseline in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, Weight, and Baseline IGA Score for Study SC1401 [ITT(1)]



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

Figure 5: Absolute Change from Baseline in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, Weight, and Baseline IGA Score for Study SC1402 [ITT(1)]



Source: Statistical Reviewer's Analysis

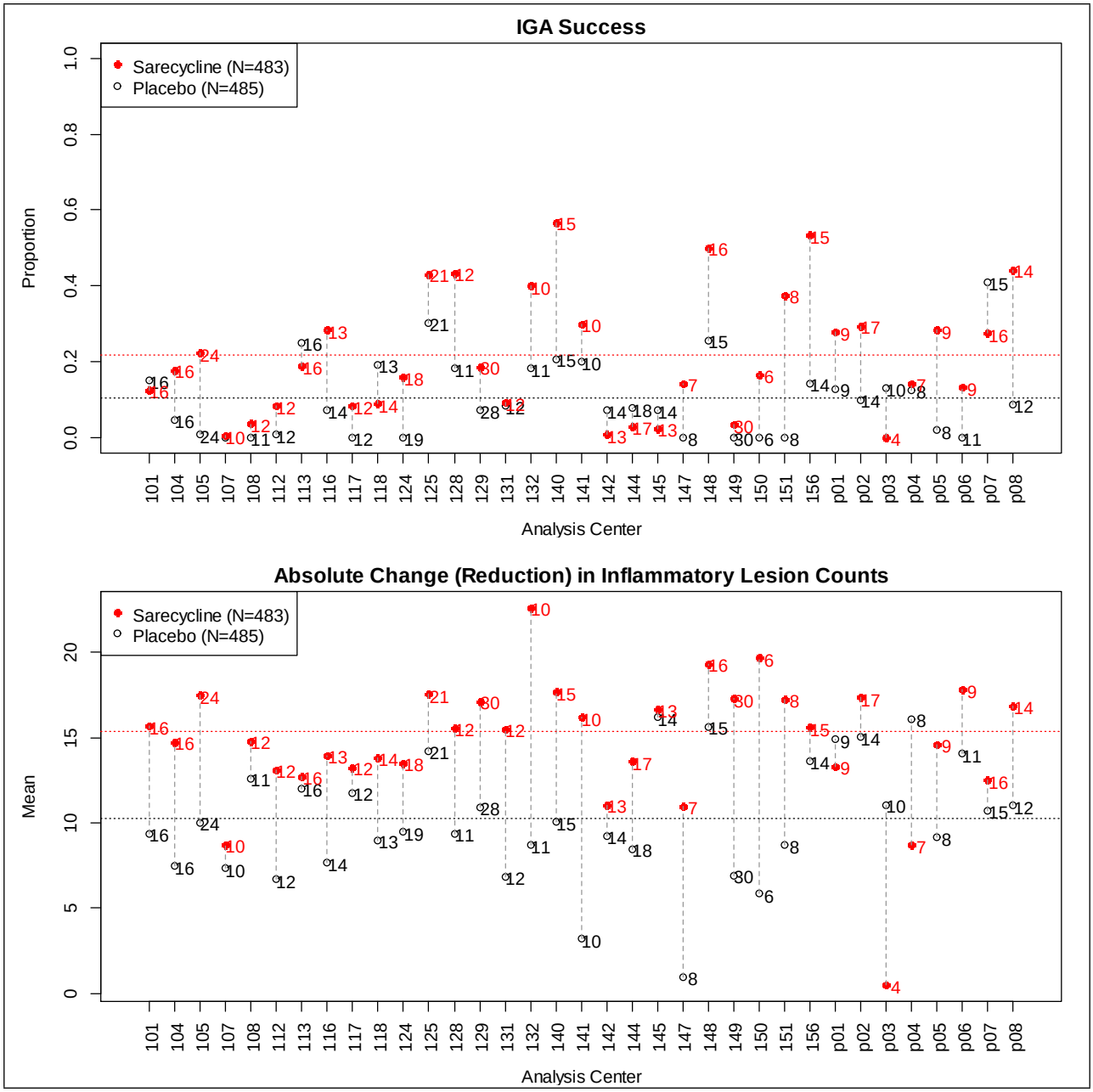
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

7.2.8.2 Center

Study SC1401 enrolled and randomized subjects from 56 centers in the United States and Study SC1402 enrolled and randomized subjects from 54 centers in the United States. The protocol specified that centers within a geographic location (i.e., the northeast, mid-west, south and west of the United States) will be pooled starting with the centers that have the lowest number of randomized subjects together such that the pooled center has a minimum of 12 randomized subjects. For Study SC1401, 27 centers remained unpooled and 29 centers were pooled to form 8 pooled centers. For Study SC1402, 40 centers remained unpooled and 14 centers were pooled to form 5 pooled centers. After the pooling procedure, the centers (pooled and unpooled) are termed “analysis centers”.

Figure 6 and Figure 7 present the results for the co-primary efficacy endpoints at Week 12 by analysis centers for Studies SC1401 and SC1402, respectively. In both trials, efficacy results varied across centers. Some centers had higher efficacy with placebo than with sarecycline. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity of the odds ratio across analysis centers at the α=0.10 level for the co-primary endpoint of IGA success at Week 12. The p-values for the Breslow-Day test across analysis centers were 0.388 for Study SC1401 and 0.191 for Study SC1402. For absolute change (reduction) from baseline in inflammatory lesion counts at Week 12, the protocol specified evaluating the treatment-by-analysis center interaction at the α=0.10 level. The non-significant p-values for the treatment-by-analysis center interaction were 0.445 for Study SC1401 and 0.805 for Study SC1402.

Figure 6: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers for Study SC1401

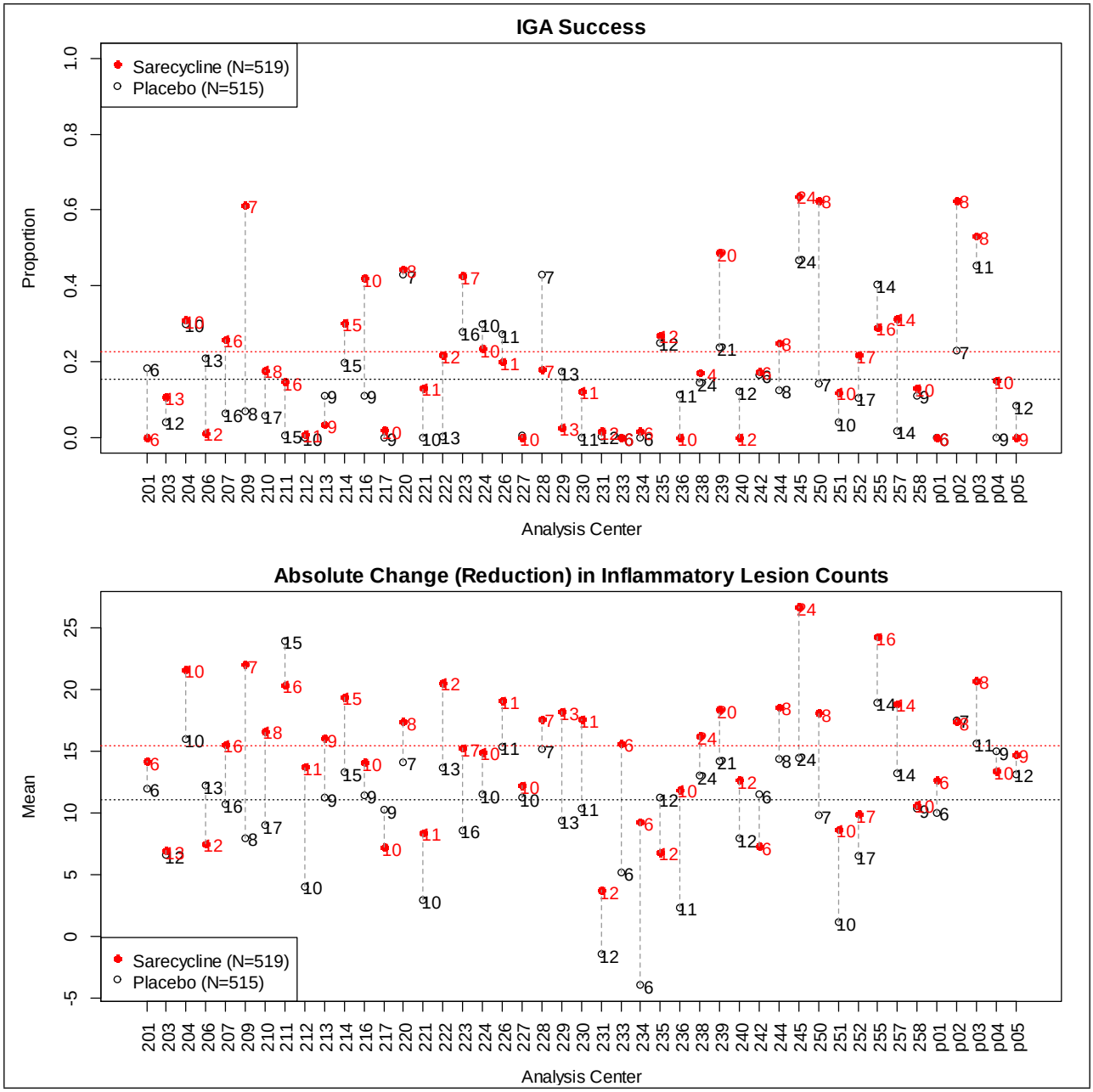


Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

(2) The dotted horizontal line denotes the overall result for each treatment arm (red for sarecycline and black for placebo).

Figure 7: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers for Study SC1402



Source: Statistical Reviewer's Analysis

(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 20 imputed datasets.

(2) The dotted horizontal line denotes the overall result for each treatment arm (red for sarecycline and black for placebo).

7.3. Review of Safety

Sarecycline was evaluated in 18 completed clinical studies, including 14 phase 1 studies (in healthy subjects and in patients with impaired hepatic or renal function), as well as a phase 2 dose-ranging study, 2 pivotal phase 3 clinical trials, and a long-term extension safety study in patients with moderate to severe acne vulgaris. The primary evidence of safety that supports the use of sarecycline for the treatment of acne vulgaris in patients 9 years of age and older is based on pooled safety data from the two multicenter, randomized, double-blind, placebo-controlled phase 3 trials and the phase 2 dose-ranging study that compared sarecycline tablets (60 mg, 100 mg, and 150 mg) and placebo tablets administered orally once daily for 12 weeks in a total of 2133 patients (safety population) 9 to 45 years of age with moderate to severe acne vulgaris.

In addition, a phase 3 long-term extension study of the two pivotal phase 3 trials was conducted (Study SC1403) that evaluated a total of 483 patients (safety population) 9 to 44 years of age with moderate to severe acne vulgaris who were exposed to sarecycline tablets 60 mg, 100 mg or 150 mg orally once daily for 40 weeks. This total number of patients included 247 patients previously exposed to sarecycline in Study SC1401 or Study SC1402 and an additional 236 patients who received placebo in Study SC1401 or Study SC1402. The safety population analyzed included the phase 2 dose-ranging subjects receiving sarecycline and the phase 3 pivotal clinical trial subjects receiving sarecycline.

7.3.1. Review of the Safety Database

Overall Exposure

The safety database of sarecycline exposure is 1820 subjects in all clinical studies (this includes 378 subjects in the phase 1 studies as seen in Table 34).

Table 34: Overall Exposure in the Clinical Development of Sarecycline

All Clinical Trial Groups	Sarecycline (N=1820)	Placebo (N= 1113)
Double Blind Pooled safety population [1]	1064	1069
Phase 1 studies [2]	378	44

[1] *combined SC1401, SC1402, PR-10411*
[2] All subjects included in Phase 1 studies

A total of 2133 patients with moderate to severe acne vulgaris were included in the Pooled Double-blind Safety Population as seen in Table 35 (sarecycline: 1064 patients; placebo: 1069 patients).

Table 35: Number of Patients Included in the Pooled Double-Blind Safety Population by Study and Treatment Group

Study Number	Sarecycline	Placebo	Total
PR-10411 (phase 2)	70	73	143
SC1401 (phase 3)	481	483	964
SC1402 (phase 3)	513	513	1026
Total	1064	1069	2133

In the Pooled Double-blind Safety Population, the mean (SD) total treatment duration as seen in Table 36 was similar in both treatment groups (sarecycline: 77.7 [19.5] days; placebo: 77.4 [20.1] days). Overall, 64.4% of the patients in both the sarecycline group (685 of 1064 patients) and the placebo group (688 of 1069 patients) were exposed to study treatment for at least 12 weeks.

Table 36: Number of Patients Included in the Pooled Sarecycline (All Doses) Safety Population by Initial Study in which Sarecycline was Received

Study Number	Number of patients in the Pooled Sarecycline (All Doses) Safety Population
PR-10411 (phase 2)	70
SC1401 (phase 3)	481
SC1402 (phase 3)	513
SC1403 (LT)	236[a]
Total	1300

a. These 236 patients received placebo during the pivotal Phase 3 trials then received open-label SEYSARA during the study 1403

A total of 1300 patients were included in the Pooled Sarecycline (All Doses) Safety Population. In this population, the mean (SD) sarecycline exposure duration was 151.1 (115.6) days. Overall, 73.6% (957 of 1300), 31.5% (409 of 1300), and 11.3% (147 of 1300) of the patients, respectively, had exposure durations of at least 12, 24, or 52 weeks.

Reviewer's comment: *Note that in the phase 2 dose-ranging study (PR-10411), subjects received a capsule formulation (0.75 and 3.0 mg/kg/day), the results of which supported the selection of Phase 3 doses of 60 mg, 100 mg, and 150 mg.*

Across the phase 1 studies, of the 422 enrolled subjects, 378 were exposed to sarecycline at single oral doses up to 500 mg or multiple oral doses up to 4 mg/kg/day (equivalent to a maximum of 400 mg/day) for up to 28 days.

Relevant characteristics of the safety population:

The phase 2 study and phase 3 trials (Studies PR-10411, SC1401, and SC1402) enrolled patients with moderate to severe facial acne. These studies included adult subjects between 18 and 45 years of age, as well as pediatric subjects who were ≥9 years of age (Studies SC1401, SC1402) or ≥12 years of age (Study PR-10411). An analysis of the double-blind clinical trial demographics is provided in section 7.2 of this review. For the pooled safety population (all doses), 1300 subjects had a mean (SD) age of 19.7 (6.5) years (range: 9 to 45 years). Adult subjects (≥18 years of age) and pediatric subjects (≥12 and <18 years of age) were approximately equally represented (648 patients [49.8%] and 639 patients [49.2%], respectively), and the remaining subjects were <12 years of age (13 patients [1.0%]). The majority of subjects were female (740 patients, 56.9%) and categorized as either white (1024 patients, 78.8%) or black/African American (192 subjects, 14.8%). In addition, most patients were non-Hispanic (937 patients, 72.1%). The mean (SD) body mass index (BMI) was 25.61 (5.88) kg/m^2 (range: 15.6 to 52.9 kg/m^2), with more patients having a baseline BMI of <25 kg/m^2 (727 patients, 56.0%) compared with a baseline BMI of ≥25 kg/m^2 (572 patients, 44.0%).

Adequacy of the safety database:

The safety database of subjects presented in this application represented 1300 moderate to severe acne subjects in the phase 2 dose-ranging and phase 3 clinical trials. In the pooled analysis of the double-blind phase 2 study and the 2-pivotal phase 3 studies, demographic characteristics at baseline were balanced between the sarecycline and placebo groups.

Subjects in the sarecycline and placebo groups ranged in age from 9 to 45 years, and a majority were white or black/African American and female. Similarly, most of the 1300 patients in the Pooled Sarecycline (All Doses) Safety Population were white or black/African American and female and ranged in age from 9 to 45 years. The demographics and baseline characteristics of the subjects enrolled in the phase 2 and phase 3 studies were representative of those of the target population intended for sarecycline treatment.

7.3.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues for the safety population.

Categorization of Adverse Events

TEAEs were coded using MedDRA, *Version 19.1*. Events with onset on or after the first dose date of test or reference article and through 30 days after the last dose of the study treatment were considered treatment emergent. The number (%) of subjects

reporting a TEAE by treatment and overall as well as the number of events reported were summarized. Gastrointestinal preferred terms were selected using relevant gastrointestinal Standardized MedDRA Queries (SMQs) and were prespecified prior to database lock. The number and percentage of subjects in the safety population who had TEAEs in the gastrointestinal SMQ were summarized by preferred term and treatment group. In addition, these TEAEs from the gastrointestinal SMQ were categorized by relationship to study treatment.

Routine Clinical Tests

Continuous clinical laboratory parameters and vital signs were summarized by treatment, analyte, and visit using descriptive statistics. Categorical laboratory parameters, classified as normal or abnormal (low or high), were summarized by treatment analyte and visit using the number (percentage) of subjects in each category. The number and percentage of subjects who had potentially clinically significant postbaseline clinical laboratory values, ECG results, or vital signs were summarized by treatment group.

7.3.3. Safety Results

Deaths

No deaths were reported in any of the 18 studies included in the clinical development program for sarecycline.

Serious Adverse Events

In subjects in the pooled safety database (all doses), the incidence of treatment-emergent SAEs was 0.8% (10 subjects). Eleven treatment-emergent SAEs (see Table 37) were reported for subjects in the sarecycline treatment groups: appendicitis (subject (b) (6)), miscarriage of partner (subject (b) (6)), abortion spontaneous (subjects (b) (6)), cellulitis and suicide attempt (subject (b) (6)), oppositional defiant disorder (subject (b) (6)), anemia and peptic ulcer (subject (b) (6)), headache (subject (b) (6)), abdominal pain (subject (b) (6)), and dehydration (subject (b) (6)).

Table 37: Incidence of Treatment-emergent Serious Adverse Events by Preferred Term (Pooled Sarecycline All Doses Safety Population)

Preferred Term	Sarecycline N=1300 n (%)
Subjects with at least 1 treatment-emergent SAE	10 (0.8)
Abdominal pain	1 (0.1)
Alanine aminotransferase increased	1 (0.1)
Abortion	1 (0.1)
Aspartate aminotransferase increased	1 (0.1)
Gamma-glutamyl transferase increased	1 (0.1)
Anemia	1 (0.1)
Headache	1 (0.1)
Crohn's disease	1 (0.1)
Dehydration	1 (0.1)
Depression	1 (0.1)
Diabetic ketoacidosis	1 (0.1)
Nephrolithiasis	1 (0.1)
Peptic ulcer	1 (0.1)
Tonsillitis	1 (0.1)

The pooled sarecycline 1.5 mg/kg/day safety population includes subjects in studies PR-10411, SC1401, SC1402, SC1403.
Adverse events were coded using MedDRA Version 19.1

Only headache was assessed by the investigator as related to study treatment. Two treatment-emergent serious adverse events ([SAEs], (peptic ulcer and abdominal pain) resulted in subject discontinuation from the study.

Reviewer's comment*: Few SAEs were reported in the sarecycline safety population. The SAEs reported were unlikely clinically related to the drug product except for the liver enzyme abnormalities. These were moderate to severe in nature and resolved when the drug product was discontinued. Liver function abnormalities can be monitored, and safety issues are presented in the label.*

Treatment Emergent Adverse Events and Adverse Reactions

In the pooled sarecycline (all doses) safety population, TEAEs were reported for 424 of 1300 subjects (32.6%) (see Table 38). The most common TEAEs (those occurring in ≥1% of subjects) in decreasing total incidence were as follows: headache (3.5%), nasopharyngitis (3.4%), nausea (3.2%), upper respiratory tract infection (2.5%), vomiting (1.6%), oropharyngeal pain (1.5%), diarrhea (1.2%), and blood CPK increased (1.2%).

Table 38: Incidence of TEAE Occurring in ≥1% of Subjects (Pooled Sarecycline All Doses safety population)

System Organ Class Preferred Term	Sarecycline N=1300 n (%)
Subjects with at least 1 treatment-emergent AE	424 (32.6)
Gastrointestinal disorders	122 (9.4)
Nausea	42 (3.2)
Vomiting	21 (1.6)
Diarrhea	16 (1.2)
Infections and Infestations	153 (11.8)
Nasopharyngitis	44 (3.4)
Upper respiratory tract infection	33 (2.5)
Vulvovaginal mycotic infection	5 (0.7%)
Vulvovaginal candidiasis	2 (0.3)
Investigations	40 (3.1)
Blood creatine phosphokinase increased	16 (1.2)
Nervous system disorders	66 (5.1)
Headache	46 (3.5)
Respiratory, thoracic and mediastinal disorders	52 (4.0)
Oropharyngeal pain	20 (1.5)

The Pooled sarecycline 1.5 mg/kg/day safety population included subjects who received sarecycline 1.5 mg/kg/day in studies PR-10411, SC1401, SC1402, SC1403
Adverse Events were coded using MedDRA Version 19.1

The incidence of vulvovaginal mycotic infection did not reach the 1 percent threshold (0.9% [7 of 740 female subjects]). However, the incidence of fungal infection TEAEs (which included the preferred terms of vulvovaginal mycotic infection, vulvovaginal candidiasis, body tinea, fungal infection, oral candidiasis, tinea infection, tinea versicolor, tinea pedis, genital candidiasis, genital infection fungal, and tinea faciei) was 1.6% (21 of 1300 patients).

The incidence of TEAEs associated with abdominal pain (which included the preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower) was 2.2% (29 of 1300 patients).

In the Pooled Double-blind Safety Population, treatment-related TEAEs were reported for 97 of 1064 subjects (9.1%) in the sarecycline group and 78 of 1069 subjects (7.3%) in the placebo group. The most common treatment-related TEAEs (i.e., those occurring in ≥1% of subjects in any treatment group) were nausea (29 subjects [2.7%] in the sarecycline group versus 16 subjects [1.5%] in the placebo group) and headache (14 subjects [1.3%] versus 16 subjects [1.5%]).

Reviewer's comment: *Narratives for all subjects with severe TEAEs were reviewed by individual study reports. No changes to the categories were made after review.*

Section 6 of the labeling will include adverse drug reactions occurring in at least 1% of

subjects with acne vulgaris in 12-week controlled clinical trials. This table will include nausea at 3.1%. The adverse drug reactions covering vulvovaginal mycotic infections (0.8%) and vulvovaginal candidiasis (0.6%) will be mentioned in the text.

The long-term evaluation of sarecycline from Day 1 through the end of final study for subjects with ≥52 weeks of sarecycline exposure (see Table 39) was 53.4% (77 of 147 subjects).

Table 39: Incidence of Common TEAE (≥%) Through the End of Final Study for Subjects ≥52 Weeks of Sarecycline Exposure (Pooled Safety Population)

Preferred Term	Day 1- end of final study for subjects on any sarecycline dose N=1300 n (%)	Day 1- end of final study for subjects with ≥52 weeks of sarecycline dose N=147 n (%)
Subjects with at least 1 TEAE	424 (32.6)	77 (52.4)
Headache	46 (3.5)	5 (3.4)
Nasopharyngitis	44 (3.4)	8 (5.4)
Nausea	12 (3.2)	6 (4.1)
Upper respiratory tract infection	33 (2.5)	7 (4.8)
Oropharyngeal pain	20 (1.5)	4 (2.7)
Vomiting	21 (1.6)	8 (5.4)
Diarrhea	16 (1.2)	2 (1.4)
Blood Creatine phosphokinase increased	16 (1.2)	2 (1.4)

The Pooled sarecycline 1.5 mg/kg/day safety population included subjects who received sarecycline 1.5 mg/kg/day in studies PR-10411, SC1401, SC1402, SC1403
Adverse Events were coded using MedDRA Version 19.1

Of the most frequently reported TEAEs (i.e., reported by ≥1% of subjects with any sarecycline exposure) through the end of final study, most individual TEAEs were reported with a similar incidence or slightly higher incidence among patients with ≥52 weeks (364 days) of sarecycline exposure than among subjects with any sarecycline exposure.

In the Pooled Sarecycline all doses safety population, the incidence of TEAEs that led to patient discontinuation was 1.9% (25 subjects). The 2 TEAEs that led to the discontinuation of more than 2 subjects were acne and urticaria (each reported for 3 subjects).

Reviewer's comment: *Incidence of TEAE that lead to discontinuation did not show any pattern of concern for these events. Only in SOC of gastrointestinal disorders (8/1300 or 0.6%) was there any consistency.*

Laboratory Findings

Laboratory findings were presented using descriptive statistics and changes from

baseline at Week 3, Week 12, and the end of the double-blind treatment period. Although minor fluctuations were observed, there were no clinically meaningful mean changes from baseline within either treatment group or differences between the 2 treatment groups for any clinical laboratory parameter.

Seven subjects (5 in the sarecycline group and 2 in the placebo group) reported a total of 10 non-serious TEAEs related to clinical laboratory results that led to study treatment withdrawal and subject discontinuation from the study. All 10 TEAEs were mild or moderate in severity. Eight of the 10 TEAEs were assessed by the investigator as related to study treatment (i.e., possibly related or related) and 9 of the 10 TEAEs resolved after treatment withdrawal.

Reviewer's comment: *The review of laboratory abnormalities in the 5 subjects that led to discontinuation revealed mostly moderate increase in hepatic enzymes. Only one subject was likely related to the study drug. None was severe enough for high risk liver injury and none lead to clinical symptoms. All resolved after drug discontinuation. There were no clinically meaningful shifts from baseline in any of the chemistry parameters.*

Vital Signs

Descriptive statistics for vital sign parameters and weight changes from baseline at Week 3, Week 6, Week 9, Week 12, and the end of the double-blind treatment period were provided in the Application.

Reviewer's comment: *Although minor fluctuations were observed, there were no clinically meaningful clinical changes from baseline for any vital sign parameter or body weight.*

Electrocardiograms (ECGs)

For the Pooled Double-blind Safety Population, descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc) and changes from baseline at the end of the double-blind treatment period for each parameter are presented by treatment group.

Reviewer's comment: *Although minor fluctuations were observed, there were no clinically meaningful ECG changes from baseline.*

QT

Sarecycline was not associated with prolongation of the corrected QT interval (QTc) in healthy subjects at a single dose of 500 mg.

Immunogenicity

There are no immunogenicity safety issues.

7.3.4. Analysis of Submission-Specific Safety Issues

Tetracycline-class antibiotics are classically associated with gastrointestinal distress, esophageal irritation, diarrhea, CNS effects (vertigo, dizziness, and tinnitus), and photosensitivity. These are labeled in Section 5 of the PI under WARNINGS AND PRECAUTIONS.

Gastrointestinal Review

In the pooled sarecycline all doses safety population, the incidence of TEAEs in the gastrointestinal SMQ (special MedDRA query) was 8% (104 subjects out of 1300). The TEAEs in the gastrointestinal SMQ (see Table 40) with an incidence ≥1% were nausea (3.2%), vomiting (1.6%), and diarrhea (1.2%).

Table 40: TEAE in the Gastrointestinal SMQ by Preferred Term (Pooled Sarecycline All Doses Safety Population)

Preferred Term	Sarecycline N=1300 n (%)
Subjects with at least 1 TEAE in gastrointestinal SMQ	104 (8.0)
Nausea	42 (3.2)
Vomiting	21 (1.6)
Diarrhea	16 (1.2)
Abdominal pain	12 (0.9)
Abdominal discomfort	9 (0.7)
Constipation	8 (0.6)
Abdominal pain upper	6 (0.5)
Dyspepsia	4 (0.3)
Gastroesophageal reflux disease	4 (0.3)
Abdominal pain lower	3 (0.2)
Gastritis	3 (0.2)
Frequent bowel movements	2 (0.2)
Duodenitis	1 (0.1)
Dysphagia	1 (0.1)
Flatulence	1 (0.1)
Gastric ulcer	1 (0.1)
Gastritis erosive	1 (0.1)
Gastrointestinal pain	1 (0.1)
Hematemesis	1 (0.1)
Hematochezia	1 (0.1)
Non-cardiac chest pain	1 (0.1)
Peptic ulcer	1 (0.1)

The Pooled sarecycline 1.5 mg/kg/day safety population included subjects who received sarecycline 1.5 mg/kg/day in studies PR-10411, SC1401, SC1402, SC1403
Adverse Events were coded using MedDRA Version 19.1

Table 41: TEAE in the Gastrointestinal SMQ by Preferred Term Grouped by Dose for Pivotal Phase 3 Clinical Trials (SC1401 and SC1402) by ITT

Preferred Term	Sarecycline N=994 n (%)		
	150 mg (N=210)	100 mg (N=639)	60 mg (N=145)
Nausea	10 (4.8)	20 (3.1)	2 (1.4)
Vomiting	2 (1.0)	9 (1.4)	2 (1.4)
Diarrhea	3 (1.4)	7 (1.1)	1 (0.7)
Abdominal pain	5 (2.4)	2 (0.3)	2 (1.4)
Abdominal discomfort	0 (0)	7 (1.1)	0 (0)
Alanine aminotransferase increased	3 (1.4)	4 (0.6)	0 (0)
CPK increased	2 (1.0)	10 (1.6)	1 (0.7)

ITT Safety Population for SC1401 and SC1402
Source: Table created with help of Dr. Matthew Guerra (Agency Biostatistician)
Reporting by MedDRA version 19.1

Reviewer's comment: *There is a slight increase in the nausea and abdominal pain from the 100 mg dose to the 150 mg dose.*

Vestibular Review

Tetracycline-class antibiotics may be associated with vestibular side effects, especially at high doses. Vestibular events (i.e., dizziness, vertigo, tinnitus, nausea, and vomiting) may cross gastrointestinal events. A thorough review of these events to separate the vestibular and gastrointestinal events was completed.

In the Pooled Double-blind Safety Population, there was a 1.0% higher incidence of vestibular TEAEs in the sarecycline group compared with the placebo group: 4.5% (48 subjects) versus 3.5% (37 subjects), respectively.

In the Pooled Sarecycline All Doses Safety Population (see Table 42, the vestibular TEAEs with an incidence ≥1% were nausea (3.2%) and vomiting (1.6%). Similar sarecycline incidence rates were seen in the Pooled Double-blind Safety Population for nausea (3.1%) and vomiting (1.3%). Both populations had the same sarecycline incidence rates for dizziness and vertigo: 0.5% and 0.1%, respectively.

Table 42: Treatment-Emergent Vestibular AE by Preferred Term (Pooled Sarecycline All Doses Safety Population)

Preferred Term	Sarecycline N=1300 n (%)
Subjects with at least 1 Vestibular TEAE	64 (4.9)
Nausea	42 (3.2)
Vomiting	21 (1.6)
Dizziness	7 (0.5)
Vertigo	1 (0.1)
Tinnitus	0 (0.0)

The Pooled sarecycline 1.5 mg/kg/day safety population included subjects who received sarecycline 1.5 mg/kg/day in studies PR-10411, SC1401, SC1402, SC1403
Adverse Events were coded using MedDRA Verson 19.1

Reviewer's comment: *Few vestibular AE occurred in the clinical trials for sarecycline. This reviewer recommends labeling the CNS effects of tetracyclines in section 5.3 of the sarecycline label.*

7.3.5. Safety Analyses by Demographic Subgroups

Studies in Patients with Impaired Hepatic or Renal Function

In Study SRC-PK-03, 6 of 24 subjects (25.0%) reported 6 TEAEs that were assessed by the investigator as study treatment-related. These were:

- Normal hepatic function group: headache (1 subject)
- Mild hepatic impairment group: headache (2 subject) and somnolence (1 subject)
- Moderate hepatic impairment group: headache (1 subject) and nausea (1 subject)

All treatment-related TEAEs were mild or moderate in severity and none resulted in subject discontinuation from the study.

In Study SRC-PK-04, 9 of 32 subjects (28.1%) reported 11 TEAEs that were assessed by the investigator as study treatment-related. These were:

- Normal renal function group: constipation (2 subjects), dry mouth, nausea, myalgia, and headache (1 subject each)
- Mild renal impairment group: myalgia and rhinorrhea (1 subject each)
- Moderate renal impairment group: diarrhea (2 separate events in the same subject) and ECG QT prolonged (1 subject)
- Severe renal impairment group: none

All treatment-related TEAEs were mild in severity and none resulted in subject discontinuation from the study.

Reviewer's comment:

Renal impairment: Study conducted in mild, moderate, and severe renal impairment indicated no dose adjustments are needed.

Hepatic impairment: Study conducted in mild, moderate, and severe renal impairment indicated no dose adjustments are needed.

7.3.6. Safety in the Postmarketing Setting

Safety Concerns Identified Through Postmarketing Experience

This drug product is not marketed in any country.

Expectations on Safety in the Postmarketing Setting

Safety issues are appropriately accessed and presented in the PI.

7.3.7. Integrated Assessment of Safety

From a safety perspective, sarecycline tablets are approvable for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. The safety of sarecycline is supported by clinical trials conducted in patients aged 9 years of age and older. The safety profile for sarecycline is generally similar to that of other tetracycline class antibiotics. Labeling is sufficient to communicate the safety issues. No PMC/PMR is recommended.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were generally consistent across trials and endpoints. There were no substantial differences in efficacy among subgroups. For handling of missing data, the results were similar across the various methods investigated to impute the missing data (see Table 26).

7.4.2. Conclusions and Recommendations

The Applicant has demonstrated that sarecycline is safe and effective for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in subjects 9 years of age and older. The dosing is based on the weight table provided in the PI. From a clinical perspective, it is recommended that the Application be approved.

8 Advisory Committee Meeting and Other External Consultation

An advisory committee meeting was not held for this product. There were no novel or complex regulatory issues that required discussion at such a public forum.

9 Pediatrics

This product triggers Pediatric Research Equity Act (PREA) considerations as a new active ingredient and has a PDUFA goal date of October 20, 2018. The Applicant submitted and followed the plan as identified in their agreed-upon initial pediatric study plan (ISE).

The application and waiver request were reviewed by the Pediatric Research Committee (PeRC) on May 23, 2018. Their recommendations are:

- The PeRC concurs with the division's plan to grant a partial waiver in pediatric patients <8 years of age because the product would be unsafe in this pediatric group (the product is in the class of tetracycline antibiotics which are contraindicated as a class due to bone/teeth staining issues in children).
- The PeRC concurs with the division's plan to grant a partial waiver in pediatric patients ages 8 to 9 years because studies would be impossible or highly impractical and the condition rarely occurs in this age group.
- The PeRC and the division reviewed the data and agree that the product has been assessed in patients 10 to 17 years of age, which is generally the standard for acne products.

The pediatric waivers are acceptable, and no pediatric studies are recommended.

13 Pages have been Withheld in Full as duplicate copy of the approved final print label (209521Orig1s000Lbl) immediately following this page

11 Risk Evaluation and Mitigation Strategies (REMS)

The benefits of treatment with sarecycline were demonstrated by meeting the co-primary endpoints of the clinical trials. Based on these results, sarecycline was found to be efficacious with an acceptable safety profile for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

Acne vulgaris is the most common dermatological disorder in the United States. It is a chronic disease of sebaceous follicles that is multifactorial in etiology. It can vary in severity according to lesion types, numbers, and extent of involvement, and can result in scarring. There are a number of topical and systemic products approved for treatment of acne vulgaris. Combination therapy utilizing agents with complementary mechanisms of action, such as an antimicrobial and a topical retinoid, is often prescribed in the management of acne vulgaris, since most anti-acne medications do not act against all of the major pathophysiologic processes, or types of lesions of acne vulgaris.

The safety profile of sarecycline is consistent with known class effects of tetracycline antibiotics that are used for the treatment of acne vulgaris. The most common TEAEs included headache, nasopharyngitis, nausea, upper respiratory tract infection, and increased blood creatinine phosphokinase. Teratogenic effects were noted in the embryofetal toxicity study in rats, which are considered class effects of tetracyclines. The Warnings and Precautions section of the PI will contain similar risk information to other tetracycline class antibiotics including teratogenic effects, *Clostridium difficile*-associated diarrhea, intracranial hypertension, central nervous system effects, photosensitivity, development of drug-resistant bacteria, and superinfection or potential for microbial overgrowth. Adverse event profiles of other tetracyclines are well established, and do not require a REMS. Sarecycline's risks can be managed with labeling and routine pharmacovigilance.

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with sarecycline use are well documented and similar to other tetracycline antibiotics. Sarecycline did not demonstrate in clinical trials that its adverse effects are different or more severe than other tetracyclines. Labeling is sufficient to manage risks associated with sarecycline.

12 Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended.

13 Appendices

13.1. References

1. Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. J Dermatol 1991; 18:489-99.

13.2. Financial Disclosure

The list of financial interest and arrangements was provided in the application. Allergan has taken the steps to minimize the potential bias of clinical study results by any of the disclosed arrangements of interest:

- The study was randomized and double-blind
- Some efficacy measures were variables derived from information recorded by the subjects during the study
- Investigators were not aware of the randomization block size
- Study payments were not made contingent upon study results

Covered Clinical Study (Name and/or Number): SC1401, SC1402, SC1403

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 166		
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): 8		
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: 6 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 1 Sponsor of covered study: 0		
Is an attachment provided with	Yes ☒	No ☐ (Request details from

details of the disclosable financial interests/arrangements:		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) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

13.3.1. Labeling

Recommended revisions to the nonclinical portions of labelling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the SEYSARA label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format which has been proposed by the Applicant. Refer to the clinical review for recommended revisions to the clinical portions of labeling in Section 8. A clean copy of the recommended nonclinical portions of labeling is also provided here.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
SEYSARA™ is a tetracycline-class drug indicated for (b) (4)

8.1 Pregnancy

Risk Summary

(b) (4) Tetracycline (b) (4) are known to cross the placental barrier; therefore, SEYSARA may be transmitted from the mother to the developing fetus. The potential risk to the fetus outweighs the potential benefit to the mother from SEYSARA use during pregnancy; therefore, pregnant patients should discontinue SEYSARA as soon as pregnancy is recognized.

(b) (4)

(b) (4)

In animal reproduction studies, sarecycline induced skeletal malformations in fetuses when orally administered to pregnant rats during the period of organogenesis at a dose (b) (4) 1.4 times the maximum recommended human dose (MRHD) based on AUC comparison. When dosing with sarecycline continued through the period of lactation, decreases in offspring survival, offspring body weight, and implantation sites and viable embryos in offspring females occurred at a dose 3 times the MRHD (based on AUC comparison) [*see Data*].

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

Data

Animal Data

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In an embryofetal developmental study in rats, sarecycline was administered to pregnant rats at oral doses up to 500 mg/kg/day during the period of organogenesis. Decreases in maternal body weight, fetal body weight and litter size and increases in the number of resorption and postimplantation loss occurred at 500 mg/kg/day (7 times the MRHD based on AUC comparison). Skeletal malformations (bent forelimb, hindlimb, and scapula) occurred at all dose levels (≥ 50 mg/kg/day, 1.4 times the MRHD based on AUC comparison).

In an embryofetal developmental study in rabbits, sarecycline was administered to pregnant rabbits at oral doses up to 150 mg/kg/day during the period of organogenesis. Excessive maternal toxicity (mortality/moribundity/abortion) occurred at 150 mg/kg/day (5 times the MRHD based on AUC comparison) and this dose group was terminated early. Maternal moribundity also occurred at 100 mg/kg/day (0.6 times the MRHD based on AUC comparison). No significant embryofetal toxicity or malformations were observed at doses up to 100 mg/kg/day (0.6 times the MRHD based on AUC comparison).

In a pre- and postnatal developmental study in rats, sarecycline was administered to maternal rats at oral doses up to 400 mg/kg/day during the period of organogenesis through lactation. Excessive litter toxicity (litter loss and stillbirth) occurred at 400 mg/kg/day (8 times the MRHD based on AUC comparison), which led to early termination of dams at parturition. Decreases in body weight and food consumption of dams during the lactation period occurred at 150 mg/kg/day (3 times the MRHD based on AUC comparison). Decreases in offspring survival and offspring body weight during the preweaning and growth period, and decreases in implantation sites and viable embryos in offspring females occurred at 150 mg/kg/day (3 times the MRHD based on AUC comparison). No significant maternal or developmental toxicity was observed at 50 mg/kg/day (1.4 times the MRHD based on AUC comparison).

8.3 Females and Males of Reproductive Potential

Infertility

In a fertility study in rats, sarecycline adversely affected spermatogenesis when orally administered to male rats at a dose 8 times the MRHD (based on AUC comparison) [*see Nonclinical Toxicology (13.1)*].

12.1 Mechanism of Action

The mechanism of action of SEYSARA in treating acne vulgaris is not known.

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

In a 2-year oral mouse carcinogenicity study and a 2-year oral rat carcinogenicity study, no drug-related neoplasms were observed in male mice at oral doses of sarecycline up to 100 mg/kg/day (approximately equal to the MRHD based on AUC comparison) or in female mice at doses up to 60 mg/kg/day (approximately equal to the MRHD based on AUC comparison), or in rats at doses up to 200/100 mg/kg/day (dose reduced from 200 to 100 mg/kg/day during the study due to increased mortality; 8 times the MRHD based on AUC comparison).

Sarecycline was not mutagenic or clastogenic in a series of in vitro and in vivo genotoxicity studies, including a bacteria reverse mutation (Ames) assay, an in vitro chromosomal aberration assay in CHO cells, the L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay, and an in vivo micronucleus assay in rats.

In a fertility and early embryonic development study in rats, sarecycline was administered to both male and female rats at oral doses up to 400 mg/kg/day prior to pairing and through the mating and postmating period. Female fertility was not affected at doses up to 400 mg/kg/day (8 times the MRHD based on AUC comparison). In sperm evaluation, decreased sperm motility, decreased sperm count and concentration, and an increase in percent abnormal sperm occurred at 400 mg/kg/day (8 times the MRHD based on AUC comparison). Male fertility was not affected at doses up to 150 mg/kg/day (4 times the MRHD based on AUC comparison).

(b) (4)

Clean version of the recommended nonclinical portions of labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
SEYSARA™ is a tetracycline-class drug indicated for (b) (4)

8.1 Pregnancy

Risk Summary

(b) (4) Tetracycline (b) (4) are known to cross the placental barrier; therefore, sarecycline may be transmitted from the mother to the developing fetus. The potential risk to the fetus outweighs the potential benefit to the mother from sarecycline use during pregnancy; therefore, pregnant patients should discontinue sarecycline as soon as pregnancy is recognized.

In animal reproduction studies, sarecycline induced skeletal malformations in fetuses when orally administered to pregnant rats during the period of organogenesis at a dose of 150 mg/day, 1.4 times the maximum recommended human dose (MRHD) based on AUC comparison). When dosing with sarecycline continued through the period of lactation, decreases in offspring survival, offspring body weight, and implantation sites

and viable embryos in offspring females occurred at a dose 3 times the MRHD (based on AUC comparison) [*see Data*].

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

Data

Animal Data

In an embryofetal developmental study in rats, sarecycline was administered to pregnant rats at oral doses up to 500 mg/kg/day during the period of organogenesis. Decreases in maternal body weight, fetal body weight and litter size and increases in the number of resorption and postimplantation loss occurred at 500 mg/kg/day (7 times the MRHD based on AUC comparison). Skeletal malformations (bent forelimb, hindlimb, and scapula) occurred at all dose levels (≥ 50 mg/kg/day, 1.4 times the MRHD based on AUC comparison).

In an embryofetal developmental study in rabbits, sarecycline was administered to pregnant rabbits at oral doses up to 150 mg/kg/day during the period of organogenesis. Excessive maternal toxicity (mortality/moribundity/abortion) occurred at 150 mg/kg/day (5 times the MRHD based on AUC comparison) and this dose group was terminated early. Maternal moribundity also occurred at 100 mg/kg/day (0.6 times the MRHD based on AUC comparison). No significant embryofetal toxicity or malformations were observed at doses up to 100 mg/kg/day (0.6 times the MRHD based on AUC comparison).

In a pre- and postnatal developmental study in rats, sarecycline was administered to maternal rats at oral doses up to 400 mg/kg/day during the period of organogenesis through lactation. Excessive litter toxicity (litter loss and stillbirth) occurred at 400 mg/kg/day (8 times the MRHD based on AUC comparison), which led to early termination of dams at parturition. Decreases in body weight and food consumption of dams during the lactation period occurred at 150 mg/kg/day (3 times the MRHD based on AUC comparison). Decreases in offspring survival and offspring body weight during the preweaning and growth period, and decreases in implantation sites and viable embryos in offspring females occurred at 150 mg/kg/day (3 times the MRHD based on AUC comparison). No significant maternal or developmental toxicity was observed at 50 mg/kg/day (1.4 times the MRHD based on AUC comparison).

8.3 Females and Males of Reproductive Potential

Infertility

In a fertility study in rats, sarecycline adversely affected spermatogenesis when orally administered to male rats at a dose 8 times the MRHD (based on AUC comparison) [*see Nonclinical Toxicology (13.1)*].

12.1 Mechanism of Action

The mechanism of action of SEYSARA in treating acne vulgaris is not known.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year oral mouse carcinogenicity study and a 2-year oral rat carcinogenicity study, no drug-related neoplasms were observed in male mice at oral doses of sarecycline up to 100 mg/kg/day (approximately equal to the MRHD based on AUC comparison) or in female mice at doses up to 60 mg/kg/day (approximately equal to the MRHD based on AUC comparison), or in rats at doses up to 200/100 mg/kg/day (dose reduced from 200 to 100 mg/kg/day due to increased mortality; 8 times the MRHD based on AUC comparison).

Sarecycline was not mutagenic or clastogenic in a series of in vitro and in vivo genotoxicity studies, including a bacteria reverse mutation (Ames) assay, an in vitro chromosomal aberration assay in CHO cells, the L5178Y/$TK^{+/-}$ Mouse Lymphoma Assay, and an in vivo micronucleus assay in rats.

In a fertility and early embryonic development study in rats, sarecycline was administered to both male and female rats at oral doses up to 400 mg/kg/day prior to pairing and through the mating and postmating period. Female fertility was not affected at doses up to 400 mg/kg/day (8 times the MRHD based on AUC comparison). In sperm evaluation, decreased sperm motility, decreased sperm count and concentration, and an increase in percent abnormal sperm occurred at 400 mg/kg/day (8 times the MRHD based on AUC comparison). Male fertility was not affected at doses up to 150 mg/kg/day (4 times the MRHD based on AUC comparison).

13.3.2. Review of carcinogenicity study reports

Study #1

Study title: P005672-HCl: A 104-week oral carcinogenicity study in mice

Study no.:	1753-022
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
CAC concurrence:	Yes

Key Study Findings

There was no treatment-related effect on mortality. A complete list of tissues was examined histopathologically. No significant test article-related neoplastic findings were noted in this study. Adverse non-neoplastic histopathological findings were noted in the kidney in high-dose males (papillary necrosis). Sarecycline was not carcinogenic when administered orally to mice once daily for 2 years.

Adequacy of Carcinogenicity Study

This carcinogenicity study was adequately conducted.

Appropriateness of Test Models

The test model was appropriate for this study.

Evaluation of Tumor Findings

There were no significant test article-related neoplastic findings under the study conditions.

Methods

Doses:	For males: 0 (vehicle control), 10, 30, and 100 mg/kg/day; For females: 0 (vehicle control), 10, 30, and 60 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 M sodium phosphate in deionized water (pH 8.0±0.1)
Basis of dose selection:	MFD
Species/Strain:	Crl:CD1® (ICR) mice
Number/Sex/Group:	60
Age:	~8 weeks at the start of dosing
Animal housing:	Animals were individually housed in suspended, stainless steel, wire-mesh type cages.
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK animals: 6/sex/group for the control group, 21/sex/group for dose groups Sentinel animals: 25/sex/group for dose groups
Deviation from study protocol:	None remarkable

Observations and Results

Mortality

Terminal necropsies were performed at Week 105. In the statistical reviewer's analysis, there was no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex. The pairwise comparisons showed no statistically significant changes in mortality between each of the treated groups and the vehicle control group in either sex (refer to the statistical review).

Table 43: Animal survival at the end of the 2-year oral mouse carcinogenicity study

		Group 1 (vehicle)	Group 2 (low dose)	Group 3 (mid dose)	Group 4 (high dose)
Male	Survival number	27	23	24	22
	Survival rate	45%	38%	40%	37%
Female	Survival number	22	21	19	18
	Survival rate	37%	35%	32%	30%

Clinical Observations

Brown discoloration of the teeth was observed in both sexes at mid dose and high dose. This is an expected effect of tetracyclines.

Body Weights

Body weight was measured weekly for the first 26 weeks and once every 4 weeks thereafter. There were statistically significant decreases in group mean body weights in high-dose males, compared to controls, on 5 occasions over Weeks 19 to 86 that ranged from -4% to -6%. There were statistically significant decreases in group mean body weights in high-dose females, compared to controls, on 16 occasions over Weeks 4 to 86 that ranged from -3% to -7%.

Feed Consumption

Food consumption was measured weekly for the first 26 weeks and once every 4 weeks thereafter. There were sporadic decreases in group mean food consumption in mid- and high-dose males and high-dose females, but such changes were not considered significantly adverse.

Serological Health Screen

A serological health screen was conducted pretest and at Months 6, 12, 18, and 24 on cohorts of up to 5 randomly selected surviving sentinel animals/sex. Serological evidence of the following was determined pretest and at Months 12, 18, and 24: pneumonia virus of mice, reovirus type 3, encephalomyelitis virus, lymphocytic choriomeningitis virus, Sendai virus, *Mycoplasma pulmonis (M. pulmonis)*, ectromelia virus, mouse hepatitis virus, minute virus of mice, and mouse parvovirus. Serological evidence of the following was determined at Month 6: *M. pulmonis*, mouse hepatitis virus, encephalomyelitis virus, and mouse parvovirus. All the results of the serological health screen (bacterial and viral) were negative.

Gross Pathology

Sarecycline-related macroscopic findings were noted in the thyroid gland, teeth, and bone: mild brown discoloration of the teeth of 1 male at 100 mg/kg/day; mild yellow discoloration of the femur bone in 1 female at 60 mg/kg/day; and mild black discoloration in the thyroid gland of 2 females at 60 mg/kg/day.

Histopathology

Peer Review: Yes

All tissues listed below were examined for all main study animals:

Adrenal, aorta, bone and bone marrow (femur, sternum), brain, clitoral gland, coagulating gland, epididymis, eye, gallbladder, gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum), GALT, Harderian gland, heart, joint (tibiofemoral), kidney, lacrimal gland, larynx, liver, lung, lymph node (mandibular, mesenteric, and regional where applicable), mammary gland (females only), nasal tissue, optic nerve, ovary, oviduct, pancreas, pharynx, pituitary, preputial

gland, prostate, salivary gland (mandibular/sublingual, parotid), sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, testis, thymus, thyroid and parathyroid glands, tongue, trachea, ureter, urinary bladder, uterus, vagina, Zymbal's gland, and gross lesions/masses.

Neoplastic:

The tumor incidence data were analyzed by the statistical reviewer. A dose response relation test (trend test) was conducted with the vehicle control group, low-, mid-, and high-dose groups. Pairwise comparison tests were conducted for vehicle control group versus each of the dose groups.

Per the FDA guidance for statistical design and data analysis of carcinogenicity studies, the statistical reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively, in trend tests, and significance levels of 0.01 and 0.05 for common and rare tumors, respectively, in pairwise comparisons. A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is <1%, and a common tumor is defined as one with tumor rate ≥1%.

The results of tumor incidence data analysis are presented in the statistical review. The tumor types with p-values ≤0.05 for trend tests and/or pairwise comparisons of vehicle control and treated groups are shown in the table below (copied from the statistical review).

Table 44: Tumor types with p-values ≤0.05 for trend test or pairwise comparison tests in the 2-year oral mouse carcinogenicity study

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Mice

(lymphoma on a per organ basis excluded)

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=60) P - Trend	10 mg/kg Low (N=60) P - VC vs. L	30 mg/kg Med (N=60) P - VC vs. M	100/60 mg/kg High (N=60) P - VC vs. H
Male	Multicentric Neoplasm	Hemangiosarcoma	2/60 (44) 0.1698	9/60 (42) 0.0201@	7/60 (41) 0.0627	7/60 (38) 0.0486@
		Lymphoma	0/60 (44) 0.4759	8/60 (44) 0.0028*	4/60 (40) 0.0474*	3/60 (38) 0.0953
Sex	**Organ Name**	**Tumor Name**	**0 mg/Kg Veh. Cont. (N=60) P - Trend**	**10 mg/kg Low (N=60) P - VC vs. L**	**30 mg/kg Med (N=60) P - VC vs. M**	**100/60 mg/kg High (N=60) P - VC vs. H**
		Hemangiosarcoma/ Hemangioma	3/60 (44) 0.1055	12/60 (42) 0.0079*	11/60 (42) 0.0151@	10/60 (38) 0.0169@
Female	Adrenal Glands	Adenoma, Subcapsular Cell	3/60 (39) 0.9540	15/60 (44) 0.0033*	8/60 (39) 0.0959	2/60 (39) 0.8208
	Multicentric Neoplasm	Hemangioma	3/60 (40) 0.8912	10/60 (43) 0.0455@	6/60 (40) 0.2407	2/60 (39) 0.8127
	Ovaries	Sarcoma, Histiocytic	0/60 (39) 0.0282@	0/60 (40) NC	3/60 (40) 0.1249	3/60 (41) 0.1297
		Sex-Cord/Stromal Tumor	1/60 (39) 0.0208@	2/60 (41) 0.5190	2/60 (39) 0.5000	6/60 (42) 0.0666

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship or 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.
@: not statistically significant at 0.025 and 0.05 level in rare tumor nor at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively.

There was no statistical significance in trend tests in any tumor types with increased sarecycline dose in either sex. The pairwise comparisons showed statistically significant increases in the incidences of the following tumors, when compared to the vehicle control: lymphoma (multicentric) in low- and mid-dose male mice (considered as rare tumor), hemangiosarcoma and hemangioma (combined) in low-dose male mice (considered as common tumor), and adrenal adenoma in low-dose female mice (considered as common tumor). Usually, for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend test and pairwise comparison test. Overall, there were no significant test article-related neoplastic findings in either sex.

Non-neoplastic:

Test article-related microscopic findings were noted in the thyroid gland of males and females at all dose levels and in the kidney of high-dose males. In the thyroid gland, minimal to mild brown to black cytoplasmic pigment accumulation was noted in the follicular epithelial cells in both males and females at all doses. The incidence and/or magnitude were dose-related. It was not considered adverse as there was no associated cytotoxicity. In the kidney, an increased incidence of papillary necrosis was noted in males at 100 mg/kg/day. The incidence of papillary necrosis noted in low- and mid-dose males and in the 3 dose groups of females were within historical control ranges.

Toxicokinetic Analysis

TK parameters were measured for sarecycline (P005672) and its 4R epimer, P005697, at Week 78 (shown in the table below, copied from the study report). There appeared to be no significant differences in systemic exposure to sarecycline and P005697 between sexes. Generally, $AUC_{0\text{-}24hr}$ values of sarecycline increased with dose in an approximately dose-proportional manner across the dose range, except that the increase was more than dose-proportional from 30 to 60 mg/kg/day in females.

Table 45: TK results for sarecycline (P005672) and its 4R epimer P005697 in the 2-year oral mouse carcinogenicity study

P005672 Toxicokinetic Parameters					
Dose (mg/kg)	Week	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (hr*ng/mL)
10	78	Male	1480	1	4930
10	78	Female	1330	1	4400
30	78	Male	3160	1	14600
30	78	Female	4430	1	16800
60	78	Female	9630	1	45200
100	78	Male	15200	1	56700

P005697 Toxicokinetic Parameters					
Dose (mg/kg)	Week	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (hr*ng/mL)
10	78	Male	25.1	1	222
10	78	Female	27.5	1	200
30	78	Male	74.8	4	620
30	78	Female	69.4	1	693
60	78	Female	191	4	1890
100	78	Male	185	4	1860

Dosing Solution Analysis

Dosing formulations prepared for the study were evaluated for concentration of the test article (sarecycline) and its 4R epimer (P005697). The results were acceptable (recovery in the range of 95%-104.7% for sarecycline).

Study #2

Study title: P005672-HCl: A 104-week oral carcinogenicity study in rats

Study no.:	1753-021
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
CAC concurrence:	Yes

Key Study Findings

Due to declining survival, the high dose was reduced from 200 mg/kg/day to 100 mg/kg/day starting from Week 62 for both sexes. All main study animals were terminated early (Week 94 for males and Week 85 for females). The dose reduction and early termination received concurrence from the Executive CAC. The increase in mortality in males was dose-related.

A complete list of tissues was examined histopathologically. No significant test article-related neoplastic findings were noted in this study. Adverse non-neoplastic histopathological findings were noted in the kidney in high dose males and females (papillary edema and necrosis). Sarecycline was not carcinogenic when administered orally to rats once daily for 2 years.

Adequacy of Carcinogenicity Study

This carcinogenicity study was adequately conducted.

Appropriateness of Test Models

The test model was appropriate for this study.

Evaluation of Tumor Findings

There were no significant test article-related neoplastic findings under the study conditions.

Methods

Doses:	For both males and females: 0 (vehicle control), 20, 60, and 200/100 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 M sodium phosphate in deionized water (pH 8.0 ± 0.1)
Basis of dose selection:	MFD
Species/Strain:	Crl:CD®(SD) rats
Number/Sex/Group:	60
Age:	~8 weeks at the start of dosing
Animal housing:	Animals were individually housed in suspended, stainless steel, wire-mesh type cages.
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK animals: 6/sex/group for the control group, 9/sex/group for dose groups Sentinel animals: 25/sex/group for dose groups
Deviation from study protocol:	Beginning in Week 62 (Day 430), the 200 mg/kg/day dose was reduced to 100 mg/kg/day. Terminal necropsies were performed on Week 94 for males and Week 85 for females.

Observations and Results

Mortality

Due to an increase in mortality rate, the high doses for both males and females were reduced from 200 mg/kg/day to 100 mg/kg/day starting from Week 62 (Day 430). Terminal necropsies were performed on Week 94 for males and Week 85 for females. The statistical reviewer's analysis showed a statistically significant increase in mortality across the vehicle control group and the three treated groups in male rats, p=0.0235. The pairwise comparison showed a statistically significant increase in mortality in high-dose males when compared to the control, p=0.0335 (refer to the statistical review).

Table 46: Animal survival at the end of the 2-year oral rat carcinogenicity study

		Group 1 (vehicle)	Group 2 (low dose)	Group 3 (mid dose)	Group 4 (high dose)
Male	Survival number	20	18	16	15
	Survival rate	33%	30%	27%	25%
Female	Survival number	20	21	22	23
	Survival rate	33%	35%	37%	38%

Clinical Observations

Brown discoloration of the teeth was noted in both sexes at doses ≥60 mg/kg/day.

Body Weights

Body weight was measured weekly for the first 26 weeks and once every 4 weeks thereafter. There were decreases in group mean body weights, compared to controls, in males at mid dose and high dose beginning Week 42 and through Week 94 (-5% and -9% at the end of treatment at mid dose and high dose, respectively), and minimal decreases in females at high dose, also beginning Week 42 and through Week 82 (-4% at the end of treatment).

Feed Consumption

Food consumption was measured weekly for the first 26 weeks and once every 4 weeks thereafter. There were no significant treatment-related changes in group mean food consumption.

Serological Health Screen

A serological health screen was conducted pretest and at Months 6, 12, 18, and prior to study termination on cohorts of up to 5 randomly selected surviving sentinel animals/sex. Serological evidence of the following was determined pretest and at Months 12 and 18, and prior to study termination: pneumonia virus, reovirus type 3, Theiler's encephalomyelitis virus, lymphocytic choriomeningitis virus, Sendai virus, *M.pulmonis*, Kilham rat virus, rat coronavirus/sialodacryoadenitis virus, Toolan's H-1 virus, and rat parvovirus. Serological evidence of the following was determined at Month 6: Sendai virus, Kilham rat virus, rat coronavirus/sialodacryoadenitis virus, Toolan's H-1 virus, rat parvovirus, and *M. pulmonis*. All serological health screens (bacterial and viral) were negative.

Gross Pathology

Test article-related macroscopic observations were noted in the bone, thyroid gland, and teeth. Yellow discoloration of the femur and black or brown discoloration of the thyroid gland were noted in all dose groups of both sexes. Brown discoloration of the teeth was noted at mid dose and high dose in both sexes.

Histopathology

Peer Review: Yes

The following tissues were examined for all main study animals adrenal, aorta, bone and bone marrow (femur, sternum), brain, clitoral gland, coagulating gland, epididymis, eye, gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum), GALT, Harderian gland, heart, joint (tibiofemoral), kidney, lacrimal gland, larynx, liver, lung, lymph node (mandibular, mesenteric, and regional where applicable),

mammary gland (females only), nasal tissue, optic nerve, ovary, oviduct, pancreas, pharynx, pituitary, preputial gland, prostate, salivary gland (mandibular/sublingual, parotid), sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, testis, thymus, thyroid and parathyroid glands, tongue, trachea, ureter, urinary bladder, uterus, vagina, Zymbal's gland, and gross lesions/masses.

Neoplastic:

The tumor incidence data were analyzed by the statistical reviewer. A dose response relation test (trend test) was conducted with the vehicle control group, low-, mid-, and high-dose groups. Pairwise comparison tests were conducted for vehicle control group versus each of the dose groups.

Per the FDA guidance for statistical design and data analysis of carcinogenicity studies, the statistical reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively, in trend tests, and significance levels of 0.01 and 0.05 for common and rare tumors, respectively, in pairwise comparisons (a tumor is defined as rare if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is <1%, and a common tumor is defined as one with tumor rate ≥1%).

The results of tumor incidence data analysis are presented in the statistical review. The tumor types with p-values ≤0.05 for trend tests and/or pairwise comparisons of vehicle control and treated groups are shown in Table 7 (copied from the statistical review).

Table 47: Tumor types with p-values ≤0.05 for trend test or pairwise comparison tests in the 2-year oral rat carcinogenicity study

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=60) P - Trend	20 mg/kg Low (N=60) P - VC vs. L	60 mg/kg Med (N=60) P - VC vs. M	200/100[#] mg/kg High (N=60) P - VC vs. H
Male	Brain	Granular Cell Tumor	0/60 (30) 0.0175*	1/60 (28) 0.4828	0/60 (28) NC	3/60 (22) 0.0697
	Urinary Bladder	Papilloma, Transitional Cell	0/60 (30) 0.0392[@]	0/60 (28) NC	1/60 (29) 0.4915	2/60 (22) 0.1742
Female	Vagina	Granular Cell Tumor	1/60 (23) 0.0421[@]	0/60 (22) 1.0000	0/60 (21) 1.0000	3/60 (21) 0.2694

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship or 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.
[@]: not statistically significant at 0.025 and 0.005 level in rare and common tumor, respectively, for tests of dose response relationship.

A statistically significant dose response was noted in male rats for the incidence of granular cell tumor in brain (considered a rare tumor). The pairwise comparison tests

showed no tumor types with a statistically significant increase in tumor incidences in sarecycline-treated groups when compared to the vehicle control group in either sex. Usually, for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend test and pairwise comparison test. Overall, there were no significant test article-related neoplastic findings in either sex.

Non-neoplastic:

Test article-related microscopic findings were noted in the kidney, liver, urinary bladder, thyroid gland, mesenteric lymph node, small intestine (duodenum, jejunum, ileum), and lung. The findings included: (1) papillary edema and necrosis in the kidney in high-dose males and females; (2) centrilobular and diffuse cytoplasmic vacuolation in the liver in high-dose males; (3) a slight increase in transitional cell hyperplasia in the urinary bladder in high-dose males and females; (4) minimal to moderate pigment accumulation in the thyroid gland in all dose groups of both sexes (not considered adverse due to absence of associated cytotoxicity); (5) vacuolation and dilated lymphatics in the mesenteric lymph node and small intestine in both sexes at mid and high doses (with no apparent associated cytotoxicity); and (6) alveolar bronchiolarization in the lung in both sexes at high dose.

Toxicokinetic Analysis

TK parameters were measured for sarecycline (P005672) and its 4R epimer, P005697, at Weeks 54 and 78 (shown in Table 8, copied from the study report). There appeared to be no significant differences in systemic exposure to sarecycline and P005697 between sexes. $AUC_{0\text{-}24hr}$ values of sarecycline increased more than dose-proportionally in both males and females at Week 78. No drug accumulation was noted between Weeks 54 and 78 for low and mid doses.

Table 48: TK results for sarecycline (P005672) and its 4R epimer P005697 in the 2-year oral rat carcinogenicity study

P005672 Toxicokinetic Parameters					
Dose (mg/kg/day)	Week	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24\ hr}$ (hr*ng/mL)
20	54	Male	7390	4	76000
	54	Female	10400	4	88300
20	78	Male	6420	4	49700
	78	Female	7280	4	49200
60	54	Male	35600	4	287000
	54	Female	53100	4	383000
60	78	Male	26200	4	180000
	78	Female	37600	4	313000
100	78	Male	44600	4	433000
	78	Female	43500	4	292000
200	54	Male	63900	8	734000
	54	Female	71400	4	816000

P005697 Toxicokinetic Parameters					
Dose (mg/kg/day)	Week	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24\ hr}$ (hr*ng/mL)
20	54	Male	120	8	1700
	54	Female	163	4	2100
20	78	Male	113	8	1360
	78	Female	141	4	1540
60	54	Male	409	4	5070
	54	Female	608	4	6850
60	78	Male	370	4	4300
	78	Female	523	8	7190
100	78	Male	652	8	8110
	78	Female	552	4	5860
200	54	Male	910	8	13300
	54	Female	1030	8	14400

Dosing Solution Analysis

Dosing formulations prepared for the study were evaluated for concentration of sarecycline and its 4R epimer, P005697. The results were generally considered acceptable (recovery in the range of 94.1% to 101.3% for sarecycline).

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

Sarecycline (also referred to as P005672, the primary analyte of interest) and its minor non-enzymatic isomer metabolite, R-sarecycline (also referred to as P005697), in plasma and urine were assayed in the clinical trials. The bioanalytical methods allowed simultaneous quantification of sarecycline and R-sarecycline using their corresponding stable isotope-labeled internal standards. Analytical methods used for the analysis of plasma samples from the clinical studies are summarized in Table 49.

Table 49: Summary of Validation Reports that Supported Plasma Sample Analyses of Sarecycline in Clinical Studies

Validation Report No. for Plasma Assays	Studies Supported
176019 (original validation)	PR-01010, PR-05011, PR-07711, PR-07811, PR-10711, PR-08212, PR-07112, and PR-12014
177054 (partial validation after modification)	PR-05011, PR-11914
183302 (partial validation after additional modification)	SRC-PK-03SRC-PK-06, SRC-PK-07
183900 (partial validation after additional modification)	SRC-PK-04, SRC-PK-08, SC1401, SC1402

All the bioanalytical methods appeared to be validated appropriately and met in-study performance criteria requirements according to the FDA Bioanalytical Method Validation Guidance. Validation accuracy, precision, and stability summary data for the bioanalytical methods are presented in Table 50 - Table 53.

Incurred sample reanalysis for plasma and urine samples was evaluated in the clinical studies, and the results of various assays were acceptable (>67% of the study samples evaluated are within ±20% of the original sample concentrations).

Table 50: Results of Bioanalytical Method Validation Report 176019 (Original Validation) for Measuring Plasma Concentrations of Sarecycline and R-Sarecycline

Analytes	**Sarecycline**	**R-sarecycline**
Matrix	Lithium Heparinized Human Plasma	
Standard curve assay range	5.00 to 4000 ng/mL	1.00 to 800 ng/mL
Precision of LLOQ	5.34%	9.73%
Intra-run precision (QCs)	1.10% to 5.34%	0.87% to 8.52%
Inter-run precision (QCs)	2.06% to 3.67%	1.75% to 5.66%
Accuracy of LLOQ	5.20%	10.0%
Intra-run accuracy (QCs)	-4.23% to 2.33%	-5.33% to 0.00%
Inter-run accuracy (QCs)	-3.30% to 1.67%	-3.33% to -0.50%
Freeze (-70 °C)/thaw (ice water bath) stability	4 cycles	
Benchtop (ice water bath) stability	5 hours	
Processed-sample reproducibility (4 °C)	72 hours	
Dilution integrity	10-fold	
Established long term frozen stability at -20°C **(Addendum report 176020)**	205 days for sarecycline; 91 days for R-sarecycline	
Established long term frozen stability at -70°C **(Addendum report 185085)**	523 days for sarecycline; 460 days for R-sarecycline	

LLOQ = lower limit of quantification
QCs = quality controls

Table 51: Results of Bioanalytical Method Partial Validation Reports for Measuring Plasma Concentrations of Sarecycline and R-Sarecycline

Report No.	**Modifications**	**Sarecycline**	**R-sarecycline**
177054	Addition of a filtration step to extraction, employing a guard column, and modification of HPLC conditions compared	Linear range: 5-4000 ng/mL Precision: 2.65% to 5.58% for QCs; 4.43% to 5.20% at LLOQ	Linear range: 1-800 ng/mL Precision: 2.51 to 7.22% for QCs; 8.09% to 8.76% at LLOQ

	to the original method	Accuracy: 1.33% to 7.33% for QCs; -5.80% to 5.60% at LLOQ	Accuracy: -3.67% to 2.17% for QCs; -2.0% to 16% at LLOQ
183302	a change in mobile phase, the use of 96-well plates	Linear range: 5-4000 ng/mL Precision: inter-run ≤ 7.05% and intra-run ≤ 9.57% (QCs and LLOQ) Accuracy: inter-run -7.40% to 7.33% and intra-run -8.80% to 9.00% (QCs and LLOQ) Dilution integrity: 20-fold	Linear range: 1-800 ng/mL Precision: inter-run ≤ 11.4% and intra-run ≤ 12.1% (QCs and LLOQ) Accuracy: inter-run -10.2% to 3.0% (QCs and LLOQ); intra-run -8.00% to 4.33% for QCs and -15.2% to -1.30% for LLOQ Dilution integrity: 20-fold
183900	a change in mobile phases and liquid chromatography conditions	Linear range: 5-4000 ng/mL Intra-run precision: 1.75% to 3.00% (QCs and LLOQ) Intra-run accuracy: 7.27% to 13.2% (QCs and LLOQ)	Linear range: 1-800 ng/mL Intra-run precision: 2.01% to 9.81% (QCs and LLOQ) Intra-run accuracy: -3.33% to 5.50% (QCs and LLOQ)

LLOQ = lower limit of quantification
QCs = quality controls

Table 52: Results of Bioanalytical Method Validation Report 176023 (Original Validation) for Measuring Urine Concentrations of Sarecycline and R-Sarecycline

	Urine pre-treated with 3% Triton (3% Triton fortified urine)		**Collection tubes pre-rinsed with a 15% Triton solution**	
Analytes	**Sarecycline**	**R-sarecycline**	**Sarecycline**	**R-sarecycline**
Standard curve assay range	100 to 100000 ng/mL	20.0 to 20000 ng/mL	100 to 100000 ng/mL	20.0 to 20000 ng/mL
Inter-run precision	≤ 5.36%	≤ 8.20%	≤ 5.70%	≤ 7.76%
Intra-run precision	≤ 3.53%	≤ 8.65%	≤ 2.80%	≤ 7.51%
Inter-run accuracy	-9.55% to -2.47%	-8.13% to -5.59%	-10.0% to -4.56%	-8.44% to -6.16%
Intra-run accuracy	-13.5% to 2.00%	-11.3% to	-13.8% to	-11.1% to -

		0.33%	1.33%	1.33%
Freeze (-70 °C)/thaw (ice water bath) stability	4 cycles			
Benchtop (ice water bath) stability	7 hours			
Processed-sample reproducibility (4 °C)	88.7 hours			
Dilution integrity	20-fold			
Established long term frozen stability **(Addendum report 176024)**	373 days at -70°C; 118 days at -20°C			

Reviewer comment:
A non-specific binding of the two analytes was discovered during initial validation runs. The Applicant found that the non-specific binding can be reduced to an insignificant level by adding Triton X-100 to the urine matrix or by pre-coating urine collection containers with Triton X-100. The Applicant then validated the 2 methods of pre-treating urine with Triton and demonstrated that they were equivalent. These validation results are acceptable to support the analysis of clinical study urine samples collected in tubes that had been pre-rinsed with a 15% aqueous solution of Triton.

Table 53: Results of Bioanalytical Method Partial Validation Report 183303 for Measuring Urine Concentrations of Sarecycline and R-sarecycline

Report No.		Sarecycline	R-sarecycline
183303 **(a change in mobile phase and the use of 96-well plates)**	Linear range	100 to 100,000 ng/mL	20.0 to 20,000 ng/mL
	Inter-run precision	1.44% to 3.17%	2.30% to 7.80%
	Intra-run precision	0.72% to 3.75%	1.63% to 9.95%
	Inter-run accuracy	1.00% to 3.67%	2.82% to 5.31%
	Intra-run accuracy	0.00% to 5.33%	-0.50% to 10.0%
	Refrigerated (4°C) benchtop stability	28.5 hours at 4°C	

13.4.2. Clinical PK Assessments

Clinical PK studies in this submission are summarized in Table 54. Three formulations were used during development: oral solution, capsules, and tablets (the to-be-marketed version). An oral solution was used in the mass balance study (PR-08212); capsules

were used in the thorough QT/QTc study (PR-07112); the to-be-market tablet formulation (60 mg, 100 mg, and 150 mg) was used in a dose proportionality study (SRC-PK-06), pivotal Phase 3 trials (SC1401 and SC1401), and studies that evaluated hepatic impairment (SRC-PK-03), renal impairment (SRC-PK-04), food effect (PR-11914), and drug-drug interaction studies (SRC-PK-07 and SRC-PK-08). The Applicant also collected PK information in another 5 clinical studies (PR-01010, PR-05011, PR-10711, PR-07711, and PR-07811) where capsules were used during drug development (

Table **55**). The Applicant demonstrated that the to-be-marketed tablet formulation was bioequivalent to capsules in Study PR-12014 (Table 56) and to oral solution in Study 11914 (Table 57).

In this review, the clinical PK discussion focuses on the PK and dose-proportionality of the to-be-marketed formulation (60 mg, 100 mg, and 150 mg tablets) in healthy subjects, and the PK in patients.

Table 54: Summary of Clinical PK Studies

Study	Study Description	Sarecycline Doses Evaluated (dosage form)	Study Population
PK			
SRC-PK-06	Single- and multiple-dose proportionality	60 mg, 100 mg, and 150 mg, QD for 7 days (tablets)	Healthy
SC-1401	Phase 3 safety and efficacy	60 mg, 100 mg, and 150 mg, QD for 12 eeks (tablets)	Patients
SC-1402	Phase 3 safety and efficacy	60 mg, 100 mg, and 150 mg, QD for 12 eeks (tablets)	Patients
ADME			
PR-08212	Mass balance study	00 mg containing 00 µCi ^{14}C-sarecycline solution)	Healthy; males
Intrinsic factor			
SRC-PK-03	Hepatic impairment	50 mg (tablet)	Healthy subjects and subjects with mild to moderate hepatic impairment
SRC-PK-04	Renal impairment	50 mg (tablet)	Healthy subjects and subjects with mild to severe renal mpairment
Extrinsic factor			

PR-11914	Food effect (150 mg tablet) and relative bioavailability (tablet vs oral solution)	50 mg tablet; solution)	Healthy
SRC-PK-07	Effect on PK of digoxin (0.25 mg tablet)	50 mg (tablet)	Healthy
SRC-PK-08	Effect on PK of oral contraceptives (tablets containing 1 mg norethindrone acetate + 20 mcg ethinyl estradiol)	50 mg (tablet)	Healthy; females
Pharmacodynamics			
PR-07112	Thorough QT/QTc study	500 mg 100 mg capsules)	Healthy
Formulation bridging			
PR-12014	Relative bioavailability/bioequivalence	00 mg (100 mg tablets and 100 mg capsules)	Healthy

Table 55: Summary of Other Clinical Studies Evaluating the PK of Sarecycline

Study Number	Study Description	Sarecycline Doses Evaluated (dosage form)	Study Population
PR-01010	Single ascending-dose	20 mg to 480 mg (20 mg and 160 mg capsules)	Healthy; males
PR-05011	Multiple ascending-dose	40 to 320 mg, QD for 7 days (20 mg, 80 mg, and 160 mg capsules)	Healthy; males
PR-10711	Food effect study	240 mg (80 mg capsules)	Healthy
PR-07711	Tolerability study	4.0 mg/kg, QD for 28 days (40 mg and 80 mg capsules)	Healthy; males
PR-07811	Phototoxicity and tolerability	240 mg (80 mg capsules)	Healthy; males

Table 56: Sarecycline PK Parameters Following Single-Dose Oral Administration of Sarecycline Tablets, 100 mg, or Sarecycline Capsules, 100 mg, in Healthy Subjects (n=26)

Parameter	Geometric mean or [Median (Range)] Sarecycline Tablets, 100 mg (Test)	Sarecycline Capsules, 100 mg (Reference)	Ratio (%) (Test: Reference)	90% Confidence Interval
C_{max}	1681	1670	100.67	97.23 to 104.23
AUC_{0-t}	29527	29599	99.76	97.01 to 102.59
$AUC_{0-\infty}$	30898	31032	99.57	96.63 to 102.60
T_{max}	[2.0 (1.0 to 4.0)]	[2.0 (1.0 to 4.0)]	NC	NC
Arithmetic mean (%CV) or [Harmonic mean]				
C_{max}	1723 (22)	1721 (24)		
AUC_{0-t}	29785 (13)	29982 (16)		
$AUC_{0-\infty}$	31149 (13)	31411 (15)		
T_{max}	2.25 (34)	2.35 (37)		
λ_z	0.0440 (14)	0.0430 (13)		
$T_{½}$	[15.7]	[16.1]		

C_{max} = maximum plasma concentration (ng/mL)
AUC_{0-t} = area under the plasma concentration (AUC) versus time curve from time 0 to the time of last measurable concentration (ng·h/mL)
$AUC_{0-\infty}$ = AUC from time 0 to infinity (ng·h/mL)
T_{max} = time of the maximum measured plasma concentration (h)
λ_z = terminal phase rate constant (1/h)
$T_{½}$ = terminal phase half-life (h)
NC = Not calculated
Source: Table 6 in study report of Study PR-12014.

Table 57: Sarecycline PK Parameters Following Single-Dose Oral Administration of Sarecycline Tablets, 150 mg or a Solution Containing 150 mg in Healthy Subjects (n=20)

Analyte	Parameter	Geometric mean or [Median (Range)] Sarecycline tablet, 150 mg, fasted (Test)	Solution containing 150 mg sarecycline (Reference)	Ratio (%) (Test:Reference)	90% Confidence Interval
Sarecycline	C_{max}	2480	2490	99.85	95.24 to 104.68
	AUC_{0-t}	41400	41100	100.74	97.14 to 104.47
	$AUC_{0-\infty}$	43200	43000	100.73	96.92 to 104.69
	T_{max}	[2.0 (1.00 to 4.00)]	[1.5 (0.33 to 3.00)]	NC	NC

AUC_{0-t} = area under the plasma concentration versus time curve (AUC) from time 0 to time t, the time of last measurable concentration (ng·h/mL).
$AUC_{0-\infty}$ = AUC from time 0 to infinity (ng·h/mL).
C_{max} = maximum plasma concentration (ng/mL).
NC = Not calculated.
T_{max} = time of the maximum measured plasma concentration (h).
Source: Table 11-12 in study report of Study PR-11914.

13.4.2.1. The Absorption, Metabolism, and Excretion Study in Healthy Subjects

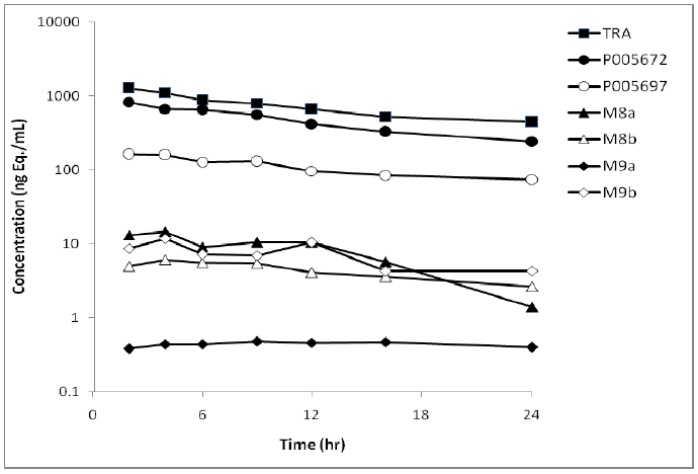
A phase 1, open-label, single dose study was conducted in 8 healthy, nonsmoking male subjects to characterize the absorption, metabolism, and excretion of sarecycline. Subjects received a single oral dose of 100 mg ^{14}C-radiolabeled (100 µCi) sarecycline (dosed as sarecycline hydrochloride in solution) under fasting conditions. Plasma and

urine sarecycline and R-sarecycline concentrations were determined using the validated liquid chromatography/mass spectrometry (LC/MS) assay. Whole blood, plasma, urine, and feces were analyzed for total ^{14}C-sarecycline-derived radioactivity content using liquid scintillation counting.

Sarecycline was the most abundant circulating radioactive moiety in plasma, accounting for approximately 64.7% of the total radioactivity (TRA) in plasma from 0 to 24 hours (Figure 8). Mean blood-to-plasma concentration ratios ranged from 0.815 to 0.900 through 36 hours post-dose. R-sarecycline was the most abundant circulating metabolite, accounting for approximately 15.1% of the TRA in plasma from 0 to 24 hours; the mean ratio of R-sarecycline to sarecycline C_{max} values was 0.03. Other minor metabolites found in plasma were M8a and M8b (N-desmethyl sarecycline or R-sarecycline), and M9a and M9b (desaturated sarecycline or R-sarecycline), accounting for about 1.13%,0.60%, 0.06%, and 0.96% of the TRA, respectively. Additional minor metabolites were not observed using radiometric detection but were detected by LC/MS.

Reviewer's comment: *The most abundant metabolite, R-sarecycline, was considered as a minor metabolite based on the mean C_{max} ratio of 0.03 compared to sarecycline.*

Figure 8: Mean Plasma Sarecycline Equivalent Concentration-Time Profiles of Total Radioactivity (TRA), Sarecycline (P005672), R-Sarecycline (P005697), and their Metabolties in Healthy Subjects



Source: Figure 4 in study report of Study PR-08212.

Mean total recovery of radioactivity was 86.7% over the period of 336 hours post-dose; 44.1% and 42.6% was recovered in urine and feces, respectively (Table 58). 24.7% and 14.9% of the administered dose was recovered unchanged in the urine and feces, respectively.

Table 58: Mean (SD) Recovery of Radioactivity Following Single-dose Oral Administration of 100 mg Sarecycline (containing 100 µCi ^{14}C-Sarecycline) in Healthy Male Subjects

	Total Radioactivity	
Sample	Amount Excreted (SD) (µg-eq)	% Dose (SD)
Urine	48,400 (5,090)	44.1 (4.62)
Feces	46,700 (5,740)	42.6 (5.24)
Total	95,100 (2,870)	86.7 (2.63)

Source: Table 9 in study report of Study PR-08212.

13.4.2.2. PK in Healthy Subjects

Single- and multiple-dose PK of sarecycline in the to-be-marketed tablet formulation (60 mg, 100 mg, and 150 mg) was evaluated in healthy subjects in a cross-over study, Study SRC-PK-06. The plasma PK parameters following once daily oral administration for 7 days are summarized in Table 59. The mean sarecycline accumulation was 1.51 to 1.58. Sarecycline C_{max} and $AUC_{0\text{-}tau}$ values increased slightly less than proportionally with increasing dose following single- or multiple-dose oral administration (Table 59). Urine sarecycline PK parameters are shown in

Table 60. The amount excreted in urine ($Ae_{0\text{-}t}$) increased proportionally with increasing dose. The mean renal clearance (CL_R) ranged from 14.6 to 14.9 mL/min on Day 1 and from 13.1 to 14.1 mL/min on Day 7.

Table 59: Single-dose and Steady-state Plasma PK Parameters of Sarecycline in Healthy Subjects

Parameter	Units	Treatment					
		Sarecycline tablets, 60 mg [Treatment A] (n=20)		Sarecycline tablets, 100 mg [Treatment B] (n=20)		Sarecycline tablets, 150 mg [Treatment C] (n=19)	
		Arithmetic mean	CV%	Arithmetic mean	CV%	Arithmetic mean	CV%
Single dose							
$C_{max, sd}$	ng/mL	1210	36.4	1790	32.5	2570	30.4
$T_{max, sd}$[a]	h	2.00[a]	0.67 to 6.00[a]	2.00[a]	0.67 to 4.00[a]	1.50[a]	0.67 to 4.00[a]
$AUC_{0-\tau, sd}$	ng·h/mL	14000	23.0	21800	24.1	32200	22.2
Steady state							
$C_{max, ss}$	ng/mL	1590	21.7	2620	25.4	3820	32.0
$T_{max, sd}$[a]	h	1.50[a]	0.67 to 4.00[a]	1.50[a]	0.67 to 6.00[a]	2.00[a]	1.00 to 4.00[a]
$AUC_{0-\tau, ss}$	ng·h/mL	20700	14.9	33800	17.4	48200	18.9
C_{avg}	ng/mL	862	14.9	1410	17.4	2010	18.9
$C_{min, ss}$	ng/mL	453	15.9	761	14.0	1060	16.3
λ_z	1/h	0.0329	15.3	0.0339	12.2	0.0334	9.6
$T_{1/2}$	h	21.9	28.1	20.7	12.8	20.9	9.9
CL/F	L/h	2.97	15.8	3.05	17.6	3.22	20.3
V_z/F	L	93.5	30.2	91.4	23.6	97.0	19.7
Single dose after dose-normalization							
$C_{max, sd}$	ng/mL	20.2	36.4	17.9	32.5	17.2	30.4
$AUC_{0-\tau, sd}$	ng·h/mL	234	23.0	218	24.1	215	22.2
Steady state after dose-normalization							
$C_{max, ss}$	ng/mL	26.5	21.7	26.2	25.4	25.5	32.0
$AUC_{0-\tau, ss}$	ng·h/mL	345	14.9	338	17.4	322	18.9
$C_{min, ss}$	ng/mL	7.56	15.9	7.61	14.0	7.05	16.3
Peak-to-trough and accumulation parameters							
Fluctuation	%	130	19.8	129	21.7	134	28.1
Swing	%	256	34.2	246	37.1	266	44.4
AI	-	1.51	11.4	1.58	11.9	1.52	13.4

[a] The median (and range) values are presented

Source: Table 11-1 in study report of Study SRC-PK-06.

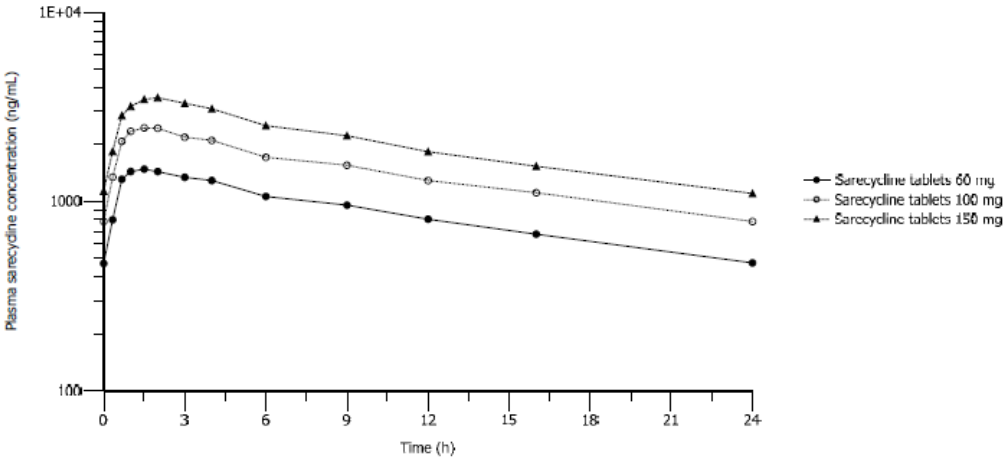
Table 60: Urine PK Parameters of Sarecycline in Healthy Subjects

Parameter	Units	Treatment					
		Sarecycline tablets, 60 mg [Treatment A] (n=20)		Sarecycline tablets, 100 mg [Treatment B] (n=20)		Sarecycline tablets, 150 mg [Treatment C] (n=19)	
		Arithmetic mean	CV%	Arithmetic mean	CV%	Arithmetic mean	CV%
Single dose							
$Ae_{0-\tau, sd}$	mg	11.8	22.9	18.6	21.2	28.1	20.9
$CL_{R, sd}$	mL/min	14.6	29.9	14.7	25.2	14.9	24.8
$fe\%_{, sd}$	%	19.60	22.9	18.59	21.2	18.71	20.9
Steady state							
$Ae_{0-\tau, ss}$	mg	16.5	18.8	28.0	16.9	36.9	19.1
$CL_{R, ss}$	mL/min	13.6	23.9	14.1	22.4	13.1	25.7
$fe\%_{, ss}$	%	27.48	18.8	27.97	16.9	24.58	19.1

Source: Table 11-2 in study report of Study SRC-PK-06.

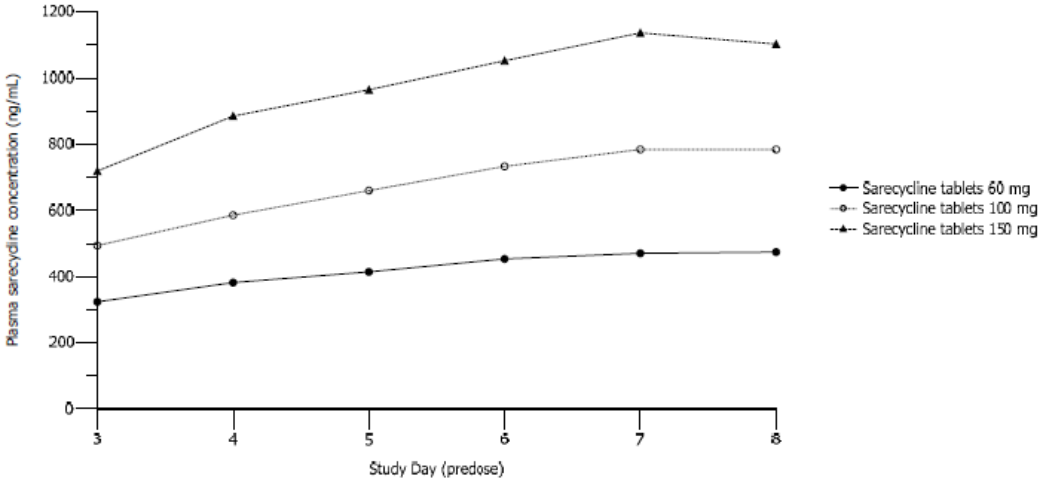
Plasma concentration-time profiles of sarecycline are shown in Figure 9. The mean plasma half-life of sarecycline was approximately 21 to 22 hours across all 3 doses. Steady-state PK were reached after 7 consecutive once-daily doses of all 3 strengths based on plasma trough concentrations (Figure 10).

Figure 9: Mean Plasma Sarecycline Concentration-Time Profiles at Steady-State Following Multiple Oral Doses (Dose 7) of Sarecycline Tablets (60 mg, 100 mg, and 150 mg) in Healthy Subjects



Source: Figure 11-2 in study report of Study SRC-PK-06.

Figure 10: Mean Trough Plasma Sarecycline Concentrations Following Multiple Oral Doses (Dose 3 Through 24 Hours After Dose 7) of Sarecycline Tablets (60 mg, 100 mg, and 150 mg) in Healthy Subjects



Source: Figure 11-3 in study report of Study SRC-PK-06.

Plasma and urine PK of R-sarecycline were also measured. Plasma R-sarecycline concentrations were substantially lower compared to the parent drug. The mean R-sarecycline:sarecycline ratios for steady state C_{max} and AUC_{0-t} remained constant with increasing dose (60 mg, 100 mg, and 150 mg, QD) at approximately 0.05 and 0.08, respectively. Therefore, no further drug-drug interaction assessment is warranted for R-sarecycline.

13.4.3. Population PK and Exposure-Response Analysis

The Applicant initially conducted population PK (PopPK) analyses (Report SRC-MS-01) for sarecycline based on data from 4 phase 1 studies (PR-10711, PR-01010, PR-05011, and PR-07112) that utilized a capsule formulation. The Applicant updated the model after including 6 additional phase 1 studies and 2 phase 3 studies (SC1401 and SC1402) that utilized the to-be-marketed tablet formulation. Based on the final PopPK model, the Applicant conducted an exposure-response (ER) analysis using efficacy data from a dose-ranging phase 2 trial and the phase 3 studies. .Text below describes the PopPK analysis that included all PK data and the ER analysis.

Methods:
The PopPK analysis was carried out using NONMEM (Version 7.3) on workstations with Intel® Core™ i7 processors, Windows 7 Professional and the GNU gfortran compiler (Version 4.5.0). Post-processing of NONMEM analysis results was carried out in R version 3.2.2. The stepwise covariate modeling (SCM) was carried out using Perl-speaks-Nonmem (PsN), version 4.2.0. Model development was carried out using first order conditional estimation with Interaction (FOCE-I).

Table 61 summarizes studies that were included in the analyses. Intensive PK sampling was performed in all the phase 1 studies. No PK data were collected in the phase 2 dose-ranging study (PR-10411). In the phase 3 studies, subjects participated in one of two PK sampling options: (1) 5 PK samples per subject at various time-points (pre-dose, 0.5 to 1 hour and 1.5 to 3 hours post-dose at Week 3, 4 to 5 hours and 6 to 8 hours at Week 12); or (2) sparse PK sampling (at any time during the visits at Week 3 and at Week 12). A total of 8400 PK observations from 562 subjects were included in the model development. Of these, 686 PK observations from 267 subjects came from the phase 3 studies.

A structural PopPK model was developed using a 2-compartment model with first order absorption with a lag time and linear elimination (the one initially developed using PK data from the four phase 1 studies) as a starting point. The initial model included body weight as a predictor of apparent clearance (CL/F) and apparent central volume of distribution (V1/F); prandial state was included as a covariate on absorption rate constant (k_a) and bioavailability (F). Different interindividual variability models as well as different residual variability models were investigated. Subject covariate relationships were examined in a stepwise procedure to examine the impact of individual subject characteristics including body weight, sex, age, renal and hepatic impairment status, absolute dose, formulations, and the number of capsules/tablets on the PK of sarecycline. The final model was qualied by numerical and graphical goodness-of-fit checks, including visual predictive check.

ER of efficacy were analyzed using phase 2 and 3 data of inflammatory lesion counts and a dichotomized IGA (dichotomized to reflect either 'success' or 'failure' with 'success' denoting at least a 2-point decrease from baseline in the IGA assessment and a score of clear [0] or almost clear [1] on the IGA assessment at Week 12).

Inflammatory lesion counts were modeled as a continuous endpoint using a longitudinal approach, incorporating observations from baseline and 4 post-baseline visits up to and including Week 12. The model was developed with terms for baseline, placebo effect, and drug effect, with each term evaluated for potential covariate effects. For the drug effect, indirect response models were considered to account for time delay between sarecycline exposure and the associated observation of the endpoint. IGA was modeled as a binary longitudinal variable using a logistic regression model. The ER analysis evaluated individual AUC_{ss} predicted by the final PopPK model (for subjects without any PK observation covariate-adjusted population-level predictions were used) and other subject characteristics, including sex, body weight, and age, on inflammatory lesion counts and IGA.

Table 61: Description of the Clinical Studies Included in the Pharmacometric Analysis

Study	Study Design	Study Population	N	N*	Treatment
PR-10711	Food effect of capsules	Healthy males and females	16	16	240 mg capsule; administered fasting or following high-fat meal
PR-01010	Placebo-controlled single dose study	Healthy males	64	48	20-480 mg, capsules, fasted
PR-05011	Placebo-controlled multiple dose study	Healthy males	56	42	40-320 mg QD X 7 days, capsules, fasted
PR-07112	TQT study	Healthy males and females	48	41	500 mg, capsule, fasted
PR-11914	Food-effect and bioavailability for tablet formulation	Healthy males and females	19	19	150 mg tablet vs. aqueous solution, fasted vs. high-fat meal
PR-12014	Relative bioavailability of tablet and capsule formulations	Healthy males and females	26	26	100 mg capsule vs. tablet, fasted
SRC-PK-03	Hepatic impairment study: Child-Pugh A, B vs. Normal (8/grp)	Healthy males and females	24	24	150 mg tablet, light meal 1-2 h predose
SRC-PK-04	Renal impairment study: Mild, Moderate, or Severe renal impairment vs. Normal (8/grp)	Healthy males and females	32	32	150 mg tablet, light meal 1-2 h predose
SRC-PK-06	Multiple dose PK study of tablet formulation at three dose-levels	Healthy males and females	24	24	60, 100, and 150 mg tablet QD, fasted X 7 days
SRC-PK-08	DDI to examine effect of sarecycline on oral contraceptive exposure	Healthy females	26	26	Oral contraceptive QD X 24 days + sarecycline 150 mg tablet QD, fasted
PR-10411	Phase 2 study	Subjects with Facial Acne Vulgaris	285	212	Placebo vs. sarecycline capsules, 0.75, 1.5, or 3.0 mg/kg QD **
SC1401, SC1402	Phase 3 study	Subjects with Facial Acne Vulgaris	~1000/each	~500/each	Placebo vs. Sarecycline 1.5 tablet mg/kg QD ***

*Subjects treated with sarecycline. ** The subjects received the same dose regardless of weight (50, 100 or 200 mg), however the weight range was limited to 52-88 kg. *** 1.5 mg/kg corresponds to: 60 mg tablet for WT 33 to 54 kg, 100 mg tablet for WT 55 to 84 kg and 150 mg tablet for WT 85 to 136 kg

Source: Table 1 in Pharmacometric Analysis Report.

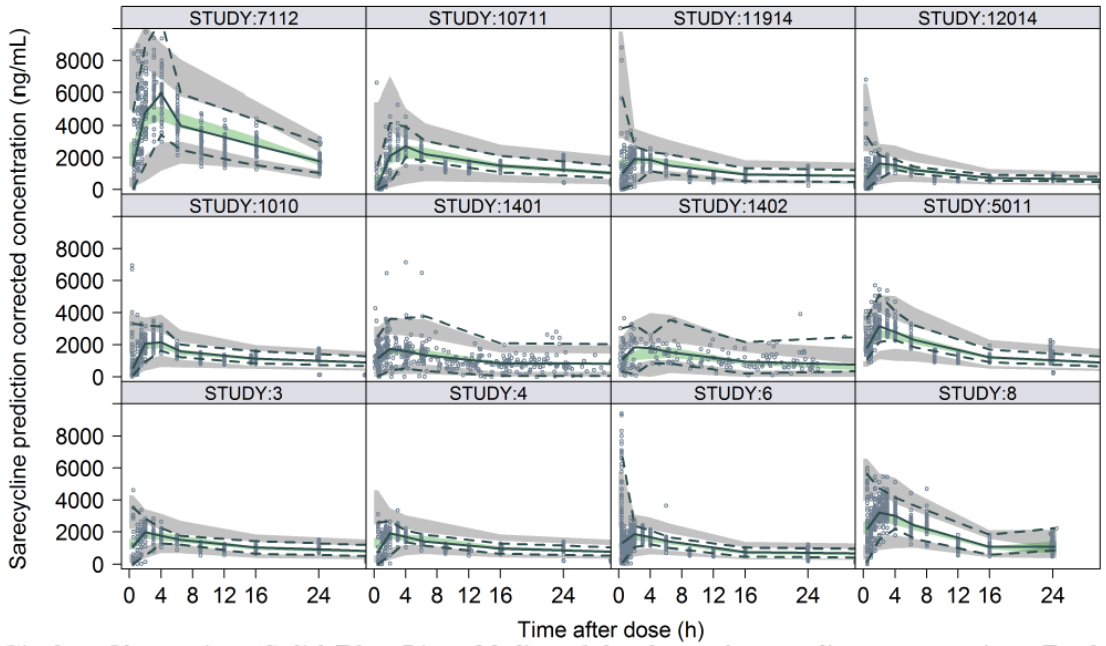
Results:

The PopPK analysis results

Plasma sarecycline PK was described by a two-compartment model with first-order absorption with a lag time and elimination. Parameter estimates of the final model (run 23) are shown in Table 62. Apparent clearance (CL/F), central volume (V1/F), peripheral volume (V2/F) and absorption rate constant (K_a) were estimated to be 3.15 L/h, 54.2 L, 15.1 L, and 3.45 h^{-1}, respectively. Inter-individual random effects of CL/F, V1/F, and K_a were estimated with coefficient of variance values of 0.034 (18.3%), 0.032 (17.8%), and 1.19 (109%), respectively. The final model fulfilled successful numerical convergence with a condition number of 247.7. Shrinkage in ETA1 (CL/F), ETA2 (V1/F) and ETA3 (k_a) for the final model were 20.2%, 27.2% and 24.2%, respectively. All parameters were estimated with sufficient precision (relative standard error <44.3%), except for the relative k_a for Study PR-11914 (relative standard error =117.7%). While this parameter should be interpreted with caution, it does not affect the individual predictions for subjects in the phase 3 studies. The prediction-corrected visual predictive check of the final PopPK model stratified by study is shown in **Error!**

Reference source not found.. Overall, the final model predicted the concentration versus time profile reasonably well.

Figure 11: Visual Predictive Check by Study based on the Final PopPK Model



Circles: Observations, **Solid Blue Line**: Median of the observed sarecycline concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed sarecycline concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al.

Source: Page 161 in Pharmacometric Analysis Report.

The parameter-covariate relationships included in the final model are prandial state and dose on both bioavailability (F) and k_a, and body weight and sex on both clearance and central volume. Compared to the initial PopPK model based on data from the first 4 phase 1 studies, body weight in this final model had less impact as a covariate on CL/F (power coefficient values 0.291 versus 0.59) and on V1/F (0.706 versus 1.3). Assuming administration of the same sarecycline dose in all subjects, subjects with the 10th and 90th percentiles of body weight in phase 3 trials (53.5 kg and 98.3 kg, respectively) are predicted to have an AUC_{ss} of 11.9% higher and 6.27% lower, respectively, compared to a subject with body weight of 78.7 kg. Therefore, body weight was determined not to be clinically important. Further exploration concluded that the impact of other covariates is also not clinically meaningful.

Table 62: Parameter Estimates of the Final PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	CL/F (L·h^{-1})	3.15	2.1	(3.02 - 3.28)
θ_2	V_1/F (L)	54.2	2.6	(51.4 - 57)
θ_3	k_a (h^{-1})	3.45	16	(2.37 - 4.53)
θ_4	Q/F (L·h^{-1})	1.18	15.8	(0.813 - 1.54)
θ_5	V_2/F (L)	15.1	6.5	(13.1 - 17)
θ_6	ALAG1 (h)	0.300	1.9	(0.288 - 0.311)
θ_8	k_a food capsule	-0.837	6.4	(-0.942 - -0.732)
θ_9	F food	-0.217	11.4	(-0.266 - -0.169)
θ_{10}	CL/F_{WT}	0.291	22.5	(0.163 - 0.42)
θ_{11}	V_1/F_{WT}	0.706	10.2	(0.564 - 0.848)
θ_{12}	k_a dose	0.456	44.3	(0.0602 - 0.853)
θ_{13}	Proportional residual variability Ph1	0.224	2.7	(0.212 - 0.235)
θ_{14}	Additive residual variability Ph1	4.17	14.6	(2.98 - 5.37)
θ_{15}	k_a food tablet	-0.670	22.2	(-0.961 - -0.379)
θ_{16}	k_a study PR-11914	17.4	117.7	(-22.7 - 57.5)
θ_{17}	Proportional residual variability Ph3	0.366	7.3	(0.313 - 0.418)
θ_{18}	Additive residual variability Ph3	136.	22.6	(75.5 - 196)
θ_{19}	F Ph3	-0.198	11.5	(-0.242 - -0.153)
θ_{20}	k_a study SC1401	-0.647	11.7	(-0.795 - -0.499)
θ_{21}	k_a study SC1402	-0.855	4.8	(-0.936 - -0.775)
θ_{22}	$CL/F_{RenalImpairment}$	-0.258	9.5	(-0.306 - -0.21)
θ_{23}	CL/F_{Male}	0.156	18.4	(0.0998 - 0.212)
θ_{24}	F_{Dose}	-0.000395	18.3	(-0.000536 - -0.000254)
θ_{25}	V_1/F_{Male}	0.347	10.2	(0.278 - 0.417)
$\omega_{1.1}$	$\omega^2_{CL/F}$	0.0336	13.7	(0.0245 - 0.0426)
$\omega_{2.1}$	$\omega^2_{CL/F,V1/F}$	0.0265	16.8	(0.0178 - 0.0352)
$\omega_{2.2}$	$\omega^2_{V1/F}$	0.0317	17	(0.0212 - 0.0422)
$\omega_{3.3}$	ω^2_{ka}	1.19	12	(0.906 - 1.46)

SE: Standard error. CI: Confidence Interval. CL/F: apparent systemic clearance. V_1/F: apparent central volume of distribution. k_a: absorption rate. V_2/F: apparent peripheral volume of distribution. Q/F: apparent intercompartment clearance. F: Bioavailability. ALAG1: Lag-time for absorption. WT: Body Weight. Ph3: Phase 3. ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$. $\omega^2_{X,Y}$: Covariance of the IIV of parameters X and Y, the corresponding correlation coefficient is derived according to $\text{cov}(\omega^2_{X,Y})/(\sqrt{\omega^2_X} \cdot \sqrt{\omega^2_Y})$.

Source: Table 11 in Pharmacometric Analysis Report.

Predicted steady-state exposure of sarecycline in patients

The summary of model-predicted individual AUC_{ss} and $C_{max,ss}$ values for the phase 3 subjects with at least 1 PK sample is shown in Table 63. The estimates are based on each subject's actual dose (either 60 mg, 100 mg, or 150 mg administered once daily for 12 weeks). Both AUC_{ss} and $C_{max,ss}$ increased as the dose group moved from 60 mg to 150 mg.

Table 63: Summary of Individual Predicted Sarecycline Exposure for Patients with PK Assessments in Phase 3 Trials (SC1401 and SC1402)

	60 mg	100 mg	150 mg	All
	(N=36)	(N=180)	(N=51)	(N=267)
AUC_{ss} (mg·h/L)				
Mean (SD)	17.4 (2.2)	25.2 (4.3)	35 (7.9)	26 (7.1)
Median (range)	17.8 (12.2 - 21.6)	24.7 (16.8 - 44.7)	34.3 (24.7 - 69.2)	25.1 (12.2 - 69.2)
$C_{max,ss}$ (mg/L)				
Mean (SD)	1.25 (0.21)	1.63 (0.33)	2.1 (0.45)	1.67 (0.42)
Median (range)	1.26 (0.78 - 1.63)	1.59 (0.962 - 3.15)	2.03 (1.39 - 4.02)	1.62 (0.78 - 4.02)
$C_{min,ss}$ (mg/L)				
Mean (SD)	0.359 (0.052)	0.578 (0.14)	0.887 (0.28)	0.607 (0.23)
Median (range)	0.353 (0.259 - 0.55)	0.547 (0.383 - 1.39)	0.785 (0.617 - 1.87)	0.552 (0.259 - 1.87)

AUC_{ss}: Area under the concentration vs. time curve at steady state. $C_{max,ss}$: Maximum concentration at steady state, $C_{min,ss}$: Minimum concentration at steady state. SD: Standard deviation.

Source: Table 12 in Pharmacometric Analysis Report.

Exposure-response analysis results

The Applicant first developed a placebo model to describe the change in lesion counts over time in subjects who received placebo. The typical placebo effect at 12 weeks was estimated to be a decrease from baseline of 11.3 inflammatory lesion counts. The drug effect was modeled using an indirect response model. A statistically significant ER relationship was found with an E_{max} model and the AUC_{ss} where half of maximum effect was estimated to be 70.0 mg·h/L. The net difference in efficacy predicted by the E_{max} model from the 25th to 75th percentiles of expected phase 3 exposure (AUC_{ss}) was 0.9 lesion counts (5.1 and 6.0 placebo adjusted change in lesion counts, respectively). The Applicant concluded that the ER relationship was relatively flat within the dose range that was evaluated, which is consistent with the observed data as shown in Figure 1. No significant ER relationship was identified for the IGA data.

Reviewer's comments:
The Applicant's ER analysis results were consistent with observed data. ER analysis for safety was not conducted, which is acceptable because there was no dose-response in the occurrence of treatment-emergent adverse events.

Applicant's rationale for the proposed dosing regimen using simulation results

Using the final PopPK model, simulations were performed with a uniform body weight distribution and without interindividual variability to illustrate the impact of body weight and dosing regimen (n=3000). Sarecycline AUC_{ss} (Figure 12) and $C_{max, ss}$ (Figure 13) values were simulated under (b) (4) the proposed dosing regimen (i.e., 60 mg, 100 mg, or 150 mg once daily for patients who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively) (b) (4)

Under the proposed dosing regimen, both AUC_{ss} and $C_{max,ss}$ increased with increasing body weight category. (b) (4) The simulated results indicated that individuals within the lower body weight range, generally children, would have been subjected to higher exposures than adults.

Table 64: Summary of Simulated Values of AUC_{ss} and $C_{max,ss}$ at the Midpoint of each Weight Category Using a Uniform Body Weight Distribution

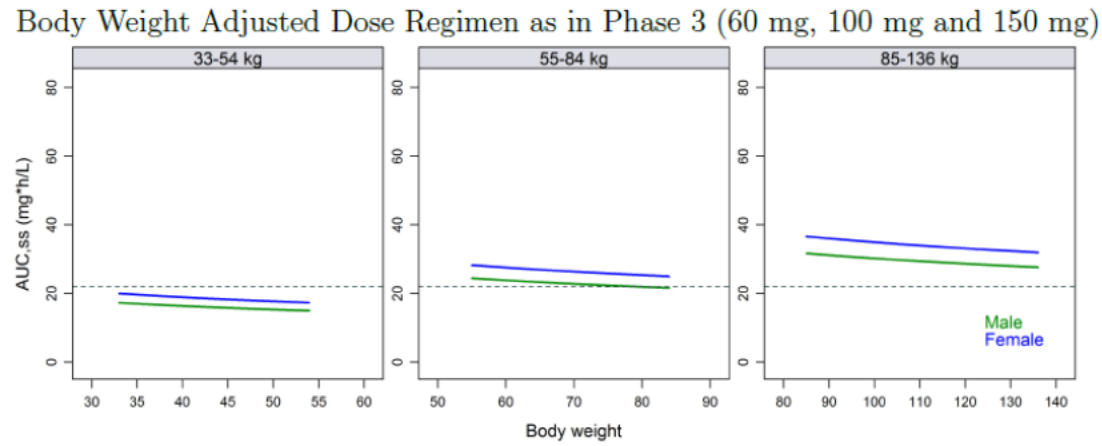
Dose Regimen	Body Weight (kg)	Dose (mg)	AUC_{ss} (mg·h/L)	$C_{max,ss}$ (mg/L)
60, 100 and 150 mg	43	60	17.2	1.31
60, 100 and 150 mg	70	100	24.6	1.65
60, 100 and 150 mg	110	150	31.7	1.95
(b) (4)				

AUC_{ss}: Area under the concentration vs. time curve at steady state. $C_{max,ss}$: Maximum concentration at steady state.

Source: Table 19 in Pharmacometric Analysis Report.

Even though the proposed dosing regimen does not result in the same level of exposure for the different weight groups, the proposed dosing regimen is reasonable: (1) the impact on efficacy due to this difference in exposure was found to be limited due to the flat efficacy-exposure response; and (2) the lower weight subjects that included pediatric patients will have had lower systemic exposure of sarecycline, which constitutes a conservative approach from a safety perspective.

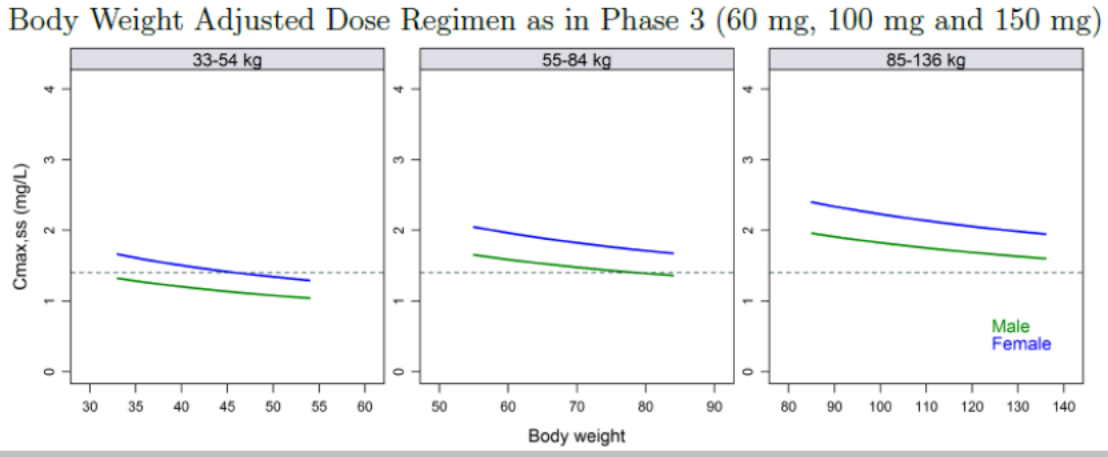
Figure 12: Simulated AUC_{ss} Using a Uniform Body Weight Distribution by Body Weight Category



(b) (6)

Source: Figure 30 in Pharmacometric Analysis Report.

Figure 13: Simulated $C_{max, ss}$ Using a Uniform Body Weight Distribution by Body Weight Category



(b) (4)

Source: Figure 31 in Pharmacometric Analysis Report.

Reviewer's comments:

The Applicant's PopPK model was appropriate for characterizing sarecycline PK. The parameters were reasonably well estimated with good precision. Although body weight was included as a covariate on clearance in the final model that described sarecycline PK, the power coefficient value of body weight on clearance is small (0.291). The identified relationship between body weight and clearance predicts that subjects with the 10th and 90th percentiles of body weight in phase 3 (53.5 kg and 98.3 kg, respectively) have an AUC_{ss} of 11.9% higher and 6.27% lower, respectively, compared to a subject with body weight of 78.7 kg. These differences are not expected to result in meaningful changes in efficacy based on the relative flat ER identified for sarecycline within the therapeutic range. This reviewer agrees that body weight was not a clinically important covariate for sarecycline.

The final PopPK analysis using both phase 1 and phase 3 data demonstrated that the impact of body weight on sarecycline exposure was less than that found in the initial PopPK analysis using phase 1 data only. Since body weight was not as influential as initially thought during drug development, the weight-based dosing regimen used in phase 3 (60 mg, 100 mg, or 150 mg tablets once daily in subjects who weighed 33 to 54

kg, 55 to 84 kg, or 85 to 136 kg, respectively) did not result in the same level of systemic exposure of sarecycline for different body weight groups; sarecycline AUC_{ss} and $C_{max,ss}$ increased as the body weight group moved from the lowest body weight group (33 to 54 kg) to the highest body weight group (85 to 136 kg). (b) (4) [redacted] *Most importantly, SEYSARA had acceptable safety and efficacy in the phase 3 trials where the proposed dosing regimen was evaluated. Therefore, the proposed dosing regimen (60 mg, 100 mg, or 150 mg tablets once daily in subjects who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively) is acceptable although sarecycline exposure vary in different body weight groups.*

Even though the proposed dosing regimen (60 mg, 100 mg, or 150 mg tablets once daily in subjects who weigh 33 to 54 kg, 55 to 84 kg, or 85 to 136 kg, respectively) is acceptable (b) (4) [redacted]

14 Division Director (Clinical)

Allergan, Inc. submitted NDA 209521 for SEYSARA (sarecycline) tablet, a new molecular entity (NME), in support of an indication for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. Sarecycline is a tetracycline-class antibiotic that exhibits antibacterial activity against clinical isolates of Propionibacterium acnes (P. acnes), including isolates with high-level resistance to the macrolide erythromycin. Additionally, sarecycline demonstrated anti-inflammatory activity in pharmacology studies.

Efficacy of sarecycline was convincingly demonstrated in two multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trials comparing sarecycline tablets (60 mg, 100 mg, and 150 mg) administered orally once daily to placebo for 12 weeks in 2002 patients age 9 to 45 years of age with moderate to severe acne vulgaris. These trials enrolled subjects with moderate to severe acne vulgaris (IGA score ≥3 [moderate], 20-50 inflammatory lesions, ≤100 non-inflammatory lesions) with a co-primary efficacy endpoint of absolute change from baseline in inflammatory lesions counts and the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point decrease from baseline at Week 12. In trial SC1401, 21.9% of sarecycline-treated subjects as compared to 10.5% of placebo-treated subjects achieved an IGA of 0/1. In trial SC1402, 22.6% of sarecycline-treated subjects achieved as compared to 15.3% of placebo-treated subjects achieved an IGA of 0 or 1.

In general, the safety profile of sarecycline was found to be similar to that of other tetracycline-class antibiotics and the Warnings and Precautions section of product labeling will convey information on risks similar to other tetracycline class antibiotics. In particular, the label will convey that sarecycline should not be used in children ≤8 years of age due to risk of permanent discoloration of teeth and interference with bone growth/formation and should not be taken during pregnancy or breastfeeding. Labeling appears adequate to convey the risks associated with sarecycline use.

I concur with the recommendation of the Division of Dermatology and Dental Products to approve NDA 209521, sarecycline tablets, a tetracycline-class drug for the treatment inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

Signature in DARRTS

15 Office Director (Office of Drug Evaluation III)

I concur with the recommendation of the Division of Dermatology and Dental Products to approve NDA 209521, sarecycline tablets, a tetracycline-class drug for the treatment inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. The recommended dose is once daily with or without food as follows:

- 60 mg for patients who weigh 33-54 kg
- 100 mg for patients who weigh 55-84 kg
- 150 mg for patients who weigh 85-136 kg

In two randomized trials involving a total of 2002 patients with acne vulgaris, sarecycline was superior to placebo in reducing inflammatory acne lesions. The safety profile of sarecycline is consistent with that of tetracycline antibiotics used for the treatment of acne. The only adverse drug reaction occurring in at least 1% of patients was nausea (3% on sarecycline vs. 2% on placebo).

The ***Warnings and Precautions*** section of product labeling will convey information on risks similar to other tetracycline class antibiotics, including: teratogenic effects, *Clostridium difficile*-associated diarrhea, central nervous system effects, intracranial hypertension, photosensitivity, development of drug-resistant bacteria, and superinfection or potential for microbial overgrowth. The risks associated with sarecycline use can be adequately managed with professional labeling and routine pharmacovigilance. A Risk Evaluation and Mitigation Strategy or REMS will not be required. Pediatric studies for ages under 9 years will be waived. There are no postmarketing commitments or required studies.

The approval of sarecycline tablets provides another treatment option for patients ages 9 years and older with inflammatory lesions of non-nodular moderate to severe acne vulgaris.

Signature in DARRTS

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
09/27/2018

YICHUN SUN
09/27/2018

YANHUI LU
09/27/2018

CHINMAY SHUKLA
09/27/2018

JIANG LIU
09/27/2018

CHANDRAHAS G SAHAJWALLA
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BARBARA A HILL
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DAVID L KETTL
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