CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217603Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader, Deputy Division Director, Division Director and Office Director Summary Review of NDA 217603

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, M.D., William Boyd, M.D., Wiley Chambers, M.D., Alexander Gorovets, M.D.
Subject	Summary Review
NDA #	217603
Applicant	Tarsus Pharmaceuticals, Inc.
Date of Submission	August 25, 2022
PDUFA Goal Date	August 25, 2023
Proprietary Name	Xdemvy
Established or Proper Name	Lotilaner ophthalmic solution, 0.25%
Dosage Form(s)	Topical
Indication	Treatment of Demodex blepharitis
Dosing Regimen	Instill one drop BID in (b) (4) for 6 weeks
Regulatory Action	**APPROVAL**

NDA 217603 Review Team Role	Reviewer
OND RPM	Ahmed Ayodeji/ Dheera Semidey
CDTL	Rhea Lloyd
Clinical Reviewer	Jennifer Harris
Nonclinical Reviewer	Muriel Saulnier/ Mukesh Summan
SPQA	Chunchun Zhang
Drug Substance	Jing Li/ Sithamalli Chandramouli
Drug Product	Elise Luoung/ Chunchun Zhang
Facilities/ Process	Sureshbabu Dadiboyena/ Kamal Tiwari
OPQ Microbiology	Karthik Krishnan / Laura Wasil
Statistical Reviewer	Wei Liu/ Greg Soon
Clinical Pharmacology Reviewer	Hyewon Kim/ Ji Ping
OND Labeling Reviewer	Derek Alberding
OSE RPM	Oyinlola Fashina
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OSI Lead	Michelle Fedowitz
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer

Administrative Background

Lotilaner is a member of the isoxazoline family of compounds. Isoxazolines are inhibitors of mite γ-aminobutyric acid (GABA)-gated chloride channels. This inhibition blocks the transfer of chloride ions across cell membranes, which results in uncontrolled neuromuscular activity. Ectoparasites exposed to isoxazolines will exhibit a spastic paralysis. In the case of Demodex mites, this paralysis leads to starvation and, ultimately, death. Isoxazolines are not inhibitors of human GABA-mediated chloride channels.

Lotilaner oral tablets were first approved in 2018 by the US Food and Drug Administration (FDA) for the treatment and control of flea and tick infestations in dogs and puppies (Credelio FDA Approval 2018). Lotilaner is also approved for the treatment and prevention of flea infestations and the treatment and control of black-legged tick infestations in cats and kittens (Credelio Cat FDA Approval 2021). Lotilaner is also authorized for use to treat flea and tick infestations in dogs and cats in the European Union (Credelio EMA Approval 2017).

Tarsus Pharmaceuticals, Inc. (Tarsus) submitted a New Drug Application (NDA) for XDEMVY™ (Lotilaner Ophthalmic Solution, 0.25%) through the 505(b)(1) pathway for approval. XDEMVY is indicated for the treatment of Demodex blepharitis.

Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The results of the clinical studies submitted in this NDA demonstrate that lotilaner ophthalmic solution, 0.25% is both statistically and clinically superior compared to vehicle in the treatment of Demodex blepharitis.

The exposure to lotilaner ophthalmic solution dosed twice per day for at least 4 weeks included 726 subjects throughout the development program. In the phase 3 trials, 415 subjects were treated with the to-be-marketed lotilaner ophthalmic solution, 0.25%. The rate of adverse events that occurred in the trials was relatively low with most occurring at a rate of no greater than 1%. The events that occurred at a higher incidence include instillation site pain (10%) Chalazion/Hordeolum (2%) and punctate keratitis. While twice as many subjects discontinued study drug in the lotilaner ophthalmic solution group compared to vehicle (6 vs.3), the low numbers and types of events do not raise any issue about the safety of the product. Additionally, lotilaner ophthalmic solution did not have any effect on the corneal endothelium through six weeks of treatment.

The benefits of treating Demodex blepharitis outweigh the risks associated with the use of lotilaner ophthalmic solution, 0.25%.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	*Demodex folliculorum* and *Demodex brevis* are two mites which are part of the normal flora of the human eyelid but may lead to anterior and posterior blepharitis, blepharoconjunctivitis, and blepharokeratitis as their density increases.	Lotilaner is an inhibitor of mite γ-aminobutyric acid (GABA)-gated chloride channels that causes paralysis which leads to starvation and, ultimately death of the mites.
Current Treatment Options	There are currently no approved treatments for Demodex blepharitis. Lid hygiene and OTC tear solutions help to decrease the mite population and improve symptoms.	Lotilaner would provide a drug product for the treatment of Demodex blepharitis.
Benefit	A reduction in collarettes directly leads to symptomatic improvement of Demodex blepharitis (irritation and eyelid erythema).	TRS-009 (Saturn-1) and TRS-010 (Saturn-2) each independently demonstrated efficacy of lotilaner by showing reduction of eyelash collarettes, mite eradication and improvement in composite score (collarettes and eyelid erythema).
Risk and Risk Management	The events that occurred at a higher incidence with lotilaner compared to the vehicle group include instillation site pain, chalazion/hordeolum and punctate keratitis.	Treatment with lotilaner for the treatment of Demodex blepharitis has an acceptable risk-benefit profile.

Product Quality

From the Integrated Quality Assessment finalized on May 18, 2023:

Qualitative and Quantitative Composition of Lotilaner Ophthalmic Solution, 0.25%

Component	Reference to Quality Standard	Function	Concentration (mg/ mL)	Concentration w/v or (g/100 mL)
Lotilaner	In-house	Active	2.5[1]	0.25
Potassium Sorbate	USP/NF[2]	Preservative	(b) (4)	(b) (4)
Edetate Disodium	USP/NF	(b) (4		
Hypromellose (HPMC (b) (4)	USP/NF			
Polyoxyl 35 Castor Oil (b) (4)	USP/NF			
Glycerin	USP			
Dibasic Sodium Phosphate (b) (4)	USP			
Monobasic Sodium Phosphate (b) (4)	USP			
Water for Injection	USP			

[1] (b) (4)

[2] Potassium sorbate that complies with the testing requirements per USP/NF

Drug Product Specifications for Lotilaner Ophthalmic Solution, 0.25%

Test Attribute	Test Method	Specifications
Appearance, Color	Visual (Current Ph Eur 2.2.2)	Slightly yellowish (b) (4) solution
Appearance, Clarity	Visual (Current Ph Eur 2.2.1)	Slightly opalescent solution (b) (4)
Identification A[1]	HPLC	Positive for Lotilaner
Identification B[1]	UV	Conform1s to Reference Standard
pH	USP <791>	(b) (4)
Osmolality (mOsm/kg)	USP <785>	
Assay Lotilaner (% of label claim)	HPLC	
Lotilaner R-enantiomer (%)	HPLC	NMT (b) (4)
Potassium Sorbate (mg/mL)	HPLC	(b) (4)
Edetate Disodium (mg/mL)	HPLC	
Related Substances of Lotilaner (%)	HPLC	
Unidentified Impurity RRT (b) (4)		NMT (b) (4)
Unidentified Impurity RRT		NMT
Unidentified Impurity RRT		NMT
Unidentified Impurity RRT		NMT
Any Individual Unspecified Impurity		NMT
Total Impurities(%)		NMT
Particulate Matter Test (Particles/mL)	USP <789>	
10 microns in diameter		NMT (b) (4)
25 microns in diameter		NMT
50 microns in diameter		NMT
Sterility[2]	USP <71>	Meets compendial acceptance criteria
Antimicrobial Effectiveness Test[3]	USP <51>	Meets compendial acceptance criteria
Minimum Fill Volume[4]	Gravimetric	NLT (b) (4) mL (Commercial presentation)
		NLT mL (Physician Sample presentation

NMT = Not More Than; NLT = Not Less Than; USP= United States Pharmacopeia; Ph Eur= European Pharmacopeia
Note: (b) (4)

(b) (4)

Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)		All steps of the drug substance synthesis, purification, raw material and in-process testing, packaging, and storage of the drug substance prior to (b) (4). CSN (non-sterile API by chemical synthesis)	Approve - Based on Previous History
		Drug substance (b) (4) and final packaging and labelling. CSN (non-sterile API by chemical synthesis)	Approve - Based on Previous History
		Drug substance analytical release testing. Stability studies LCP (Laboratory, Chemical/Physical Testing)	Approve - Based on Previous History
		Drug substance XRPD testing LCP ((Laboratory, Chemical/Physical Testing)	Approve - Based on Previous History
		Drug substance microbiological testing. LMN (Laboratory, Microbiological-non-sterility testing	Approve - Based on Previous History
		Drug product manufacture including formulation, (b) (4), fill and finish; In-Process and Release testing; Stability storage and testing; Procurement of (b) (4) primary packaging components (device constituent parts) (i.e., Bottles, tips and caps); Procurement and release testing of excipients and raw materials SLQ (Sterile liquid (other than suspensions & emulsions), MIS (Not elsewhere classified)	Approve - Based on PAI
		Manufacture and supplier of (b) (4) primary packaging components (device constituent parts) (i.e.bottles, tips and caps) MIS (Not elsewhere classified)	No Evaluation Necessary
		(b) (4) and control of primary packaging components (device constituent parts) MIS (Not elsewhere classified)	No Evaluation Necessary
		(b) (4) and control of primary packaging components (device constituent parts) MIS (Not elsewhere classified)	No Evaluation Necessary

OPQ Recommendations and Conclusion on Approvability

NDA 217603, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Xdemvy (lotilaner ophthalmic solution), 0.25%. All information requests and review issues have been addressed. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on April 24, 2023.

The drug product is regulated as a drug device combination product per the Genus decision. CDRH confirmed that no CDRH GMP/QS consults is necessary for this product on Sep 28, 2022. Therefore, NDA 217603 is recommended for approval from Product Quality perspective.

The statement at the end of this paragraph has been recommended by OPQ to be included in the action letter; however, the clinical group does not agree that drug product changes can be accepted based on drug substance biocompatibility for topical ophthalmic products. This statement:

> The comparability protocol for the drug substance and the proposed submission category of CBE-30 are acceptable. The drug product comparability protocol as provided, can be part of the Drug Substance comparability protocol since the demonstration of equivalence is usually done as part of the Drug Substance comparability protocol.

will not be included in the action letter.

Nonclinical Pharmacology/Toxicology

From the Nonclinical review dated 5/9/23: The nonclinical studies conducted by the Applicant support the approval the NDA. The NDA is approvable from nonclinical pharmacology/toxicology standpoint.

Brief Discussion of Nonclinical Findings
Lotilaner is an ectoparasiticide and insecticide initially developed as a veterinary product for control of flea and tick infestations and has also been found effective against Demodex mites. The nonclinical safety of Lotilaner and Lotilaner Ophthalmic Solution, 0.25% were evaluated in the rabbit, rat and dog which were considered appropriate. In the preclinical development studies, Lotilaner is also referred to as TP-03, IOB920 and AHC2224920 as the same active compound.

Pharmacology
Key Findings:

- Isoxazolines, including Lotilaner, are specific inhibitors of (GABA)-gated chloride channels (GABACls) paralyzing the nervous system of insects or arachnids leading to their death. Lotilaner is not an inhibitor of mammalian GABACls when tested at up to 30 µM (18 µg/mL) *in vitro*.
- Lotilaner was evaluated for off-target activity *in vitro* at a concentration of 10 µM (6 µg/mL) against a comprehensive panel of enzymes, ion channels, and receptors. There were no clinically relevant findings.

Safety Pharmacology:

Key Findings:

The central nervous system, respiratory and cardiovascular assessments of Lotilaner were evaluated in GLP studies *in vitro* (hERG assay) and *in vivo* in rats and dogs. No clinically relevant adverse effects were noted in any of the studies.

PK/ ADME/ TK:

Key Findings:

Absorption

In Dutch belted rabbits dosed twice daily for 8 days consecutively with (b) (4) mg/eye/day/OU Lotilaner Ophthalmic Solution, 0.25%, the test article accumulated up to 7-fold in the blood after multiple administrations with mean C_{max} observed at 6 h post-dose. On Day 8, the systemic exposure decreased steadily through 10 days post last dose. Lotilaner $T_{1/2}$ in blood was over 2 days (> 57 h) with an AUC_{last} of 617 h.ng/mL and an apparent volume of distribution consistent with large tissue distribution of the drug product.

In the ocular tissues, lotilaner $T_{1/2}$ was over 11 days (up to 274 h) consistent with the accumulation of the test compound after multiple exposures compared to a single exposure. The average C_{max} was the highest in the eyelid margins and palpebral conjunctiva followed by the cornea, bulbar conjunctiva, lachrymal glands, and the iris/ciliary body. Overall, the data indicated that inferior and superior eyelid margins were prone to drug accumulation, coupled with the lowest clearance in these tissues and an AUC_{inf} 10-fold higher than in all other ocular tissues. Low clearance was also found in the tears that may also be prone to test article accumulation.

Distribution

In vitro, Lotilaner at 5 µM (3 µg/mL) was highly plasma protein bound (≥ 99%) in all species studied including humans. In rats and dogs after oral exposure to Lotilaner, tissue distribution occurred mainly in liver > fat > muscle.

Metabolism

In vitro, Lotilaner was metabolically stable in hepatocytes from mouse, rat, rabbit, dog, monkey, and human. This was confirmed *in vivo* in rats and dogs. Negligible amounts of metabolites were identified in blood, urine, and tissue samples with the parent compound being predominant. Metabolite profiling was not conducted in any species including humans due to the observed *in vitro* hepatocyte stability and the absence of liver metabolism.

Excretion

The excretion of unchanged product in rats and dogs after oral exposure was mostly fecal with a few percentages recovered in the urine. A cat study with Lotilaner by the oral route indicated bile excretion of unchanged product, reabsorption, and recirculation that may explain the long $T_{1/2}$ and accumulation of Lotilaner in tissues observed in the animal studies.

Based on the metabolism and excretion results presented herein, there was no disproportional or unique metabolite(s) in humans anticipated compared to the species used for toxicity studies, i.e., the rat, the rabbit, and the dog.

Ocular and Systemic Toxicity

Key Findings:

- In two ocular GLP toxicity studies with Lotilaner Ophthalmic Solution, 0.25%, in the Dutch Belted rabbit and in the Beagle dog for 6 and 9 months, respectively, the no observed adverse effect level (NOAEL) was the highest dose tested of (b) (4) µg/eye/day/OU, i.e., (b) (4) µg/animal/day. There were no test-article related findings at any dose in either species.

  In the rabbit, at the NOAEL, mean C_{max} and AUC_{0-24} values on Day 182 were 251 ng/mL and 5,385 ng*hr/mL, respectively, in males and females combined (no gender differences in exposure). In the dog, at the NOAEL, mean C_{max} and AUC_{0-24} values on Day 273 were 403 ng/mL and 7,790 ng*hr/mL, respectively, in males and females combined (no gender differences in exposure).

  Ocular safety margins to the clinical dose are 2.66X in both rabbit and dog, based on direct dose comparison, while systemic safety margins are (b) (4) X with the rabbit and (b) (4) X with the dog, based on mg/m^2 equivalent. These safety margins were found to be acceptable by this reviewer.

- The systemic toxicity of AHC 2224920 was assessed by daily oral exposure for 13 weeks in the rat and once *per* month for 8 months in the Beagle dog in a GLP fashion. Test-article related microscopic findings were noted in body weight, skin/mucosa, ovary, lung, adrenal, pituitary (males only) and thymus in rats. Mortality due to early sacrifice of moribund animals occurred at 60 mg/kg/day in female rats and at ≥40 mg/kg/day in male rats. However, none of the findings were clinically relevant as they occurred at doses > 500X the therapeutic dose in mg/m^2 equivalent.

  There were no adverse findings in the dog up to the highest dose tested of 215 mg/kg which corresponded to a systemic safety margin > 20,000X with the therapeutic dose in mg/m^2 equivalent. Considering the exposure to Lotilaner was relatively constant in the dog study by oral exposure, this reviewer found the design of monthly administration in the dog acceptable for assessing systemic toxicity in the context of a daily ocular exposure in humans for 6 weeks.

Genotoxicity

Key Findings:

AHC 2224920 was negative for genotoxic potential in a complete battery of genotoxicity GLP studies (i.e., Ames test, *in vitro* chromosome aberration test in cultured human lymphocytes and *in vivo* micronuclei assay in rats).

Carcinogenicity

Key Findings:

No studies were performed. The Sponsor provided a rationale for not conducting carcinogenicity studies with Lotilaner that was found to be acceptable by this reviewer (see "Carcinogenicity Section").

Reproductive Toxicity

Key Findings:

- In an embryo-fetal toxicity in the rat with AHC 2224920 by oral gavage at doses of 9, 18 and 50 mg/kg/day, the NOAEL for maternal and fetal toxicities was 18 mg/kg/day providing a safety margin based on dose of (b) (4) X (in mg/m^2 equivalent) with the Maximum Recommended Human Ophthalmic Dose (MRHOD) of (b) (4) mg/kg for a 60 kg human. Above NOAEL, the test article was not tolerated resulting in marked body weight loss and early termination of multiple females at 50 mg/kg. There was a marked effect on mean fetal weight at 50 mg/kg/day and there was an indication of a developmental delay characterized by an increased number of fetuses with incomplete ossification of individual bones of the skeleton. A test article related malformation of situs inversus of the thoracic and abdominal viscera was observed in 1 fetus from this group. No TK data were produced in this study.
- In an embryo-fetal toxicity in the rabbit with AHC 2224920 by oral gavage at doses of 2.5, 7.5 and 20 mg/kg/day, the maternal NOAEL was 7.5 mg/kg/day (C_{max} = 3,200 ng/mL; AUC_{0-24} = 56,200 h*ng/mL) and the fetal NOAEL was 20 mg/kg/day (C_{max} = 8,680 ng/mL; AUC_{0-24} = 170,000 h*ng/mL). These NOAELs provided safety margins based on dose of (b) (4) (in mg/m^2 equivalent) for maternal and fetal toxicities, respectively, considering a MRHOD of (b) (4) mg/kg for a 60 kg human. Decreased food consumption during the dosing phase was noted for animals administered 20 mg/kg/day.
- There was no designated fertility study, however the results of the 2-generation study in the rat suggested that the NOAEL for male fertility was 20 mg/kg/day under the conditions of the study, which provided a safety margin based on dose of (b) (4) X (in mg/m^2 equivalent) with the MRHOD of (b) (4) mg/kg for a 60 kg human.

Special Studies

Key Findings:

- AHC 2224920 was minimally irritating to the eye after instillation of 100 mg into the conjunctival sac of male New Zealand White rabbits in a 3-day ocular irritation test.
- AHC 2224920 triggered no alert for respiratory and skin sensitization after *in silico* analysis. The absence of skin sensitization was confirmed with a Local Lymph Node Assay in the mouse.
- AHC 2224920 was classified as a non-irritant for the skin based on the Draize classification system in the rabbit.
- In an acute dermal toxicity test with rats, the median lethal dose of AHC 2224920 exceeded 2000 mg/kg.

RECOMMENDATIONS

The clinical dose ((b) (4) mg/eye/day) and the length (6 weeks) of the therapeutic exposure were supported by 2 ocular and 2 systemic toxicity studies of adequate length and performed under GLP conditions. Safety pharmacology and genotoxicity batteries were complete and acceptable as were embryofetal toxicity studies in 2 species, i.e., the rat and the rabbit, and a 2-generation reproductive toxicity study in the rat to cover both male fertility and reproductive and developmental toxicity of the product. The request for lack of carcinogenicity studies was also justified. Nasal turbinate and nasopharynx were not examined under the microscope in any of the ocular studies which was a drawback to the complete evaluation of the potential ocular toxicity of Lotilaner Ophthalmic Solution, 0.25%, but does not influence the decision on approvability of this product. No clinical signs were observed in any animal study that could suggest nasal cavities and/or throat irritation. The product is approvable from a pharmacology and toxicology perspective.

Clinical Pharmacology

From the Clinical Pharmacology review dated 4/20/23:

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted from Study TRS-012, multiple-dose PK study in healthy subjects as well as the PK findings from phase 3 pivotal trials, Studies Saturn-1 and Saturn-2 in support of NDA 217603. The clinical pharmacology assessment found the application acceptable to support approval from a clinical pharmacology perspective.

2.1 Pharmacology and Clinical Pharmacokinetics

Absorption

Following a single topical ocular administration of Lotilaner, 0.25% the median lotilaner whole blood lag time (T_{lag}) was 0.5 hour, indicating a delayed absorption after topical administration. Maximum systemic exposure after topical application occurs 2 hours after a single administration and by 1 hour on the last day of 42 days of treatment. In healthy subjects, the peak concentration (C_{max}) was 0.596 ng/mL and total exposures of lotilaner 0.25%, AUC_{0-12} and AUC_{0-24}, in whole blood were 5.75 ng·hr/mL and 9.98 ng·hr/mL, respectively. These values increased after repeated ocular BID administration over 40 days, with C_{max} of 17.8 ng/mL and AUC_{0-24} of 293 ng·hr/mL.

Distribution

No distribution data for lotilaner is available in human. Lotilaner plasma protein binding was high (> 99.9%) in human plasma. The actual mean value of unbound was 0.0732 % for lotilaner (5 µM) after dialysis in human plasma. The partitioning of lotilaner to human blood cells ranged 0-20% and generally approximately closer to 10%.

Metabolism

Negligible metabolism of lotilaner was observed in blood in rats and dogs. *In vitro* study for the evaluation of lotilaner metabolic stability in human liver microsome indicated limited or no metabolism of lotilaner following 60-minute incubation. There is no lotilaner metabolism study in humans.

Excretion

The terminal plasma elimination half-life of Lotilaner following BID dosing in both eyes for 40 days was approximately 1400 hours (58.3 days). However, the effective half-life, which is based on the accumulation ratio over the dosing interval of 12 hours, was 264 hours (11 days). The PK results from Study TRS-012 indicated that lotilaner systemic exposure (C_{trough}) in healthy subjects did not reach a steady state after twice daily dosing for 42 days. Per ADME studies in rats and dogs, lotilaner is primarily excreted through the biliary route whereas the renal route was a minor route of elimination.

Specific Populations

From a perspective of safety, given minimal systemic exposure following topical administration to eye, dose adjustment is not warranted in subpopulations based on the commonly known intrinsic factors.

Drug-Drug Interaction

In vitro studies showed that lotilaner is not metabolized by CYP enzymes. In *in vitro* setting, lotilaner showed direct inhibition of a few CYP enzymes at higher concentrations than clinically relevant range. Therefore, the drug-drug interaction potential of lotilaner through CYP enzymes is minimal.

Review Issue	Recommendations and Comments
Dosing in patients (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. There is no difference between the clinical trial formulation and the to be marketed formulation.

Clinical Efficacy

Clinical data for the two Phase 3 studies SATURN-1 and SATURN-2 are the primary basis of the clinical efficacy assessment. The trials shared identical inclusion/exclusion criteria, efficacy assessments and methods (i.e., scoring scales and evaluation procedures), randomized study drugs (Lotilaner or vehicle), and treatment durations; the efficacy endpoints evaluated in each study were also nearly identical.

Efficacy Results – Primary Endpoint

Endpoints for Demodex blepharitis that were used to evaluate the efficacy of lotilaner ophthalmic solution include:

- Collarette grade = 0 (meaning the presence of 2 or less lashes with collarettes on the upper eyelid of the analysis eye)
- Mite eradication
- Lid erythema = 0

Study TRS-009 (SATURN-1) had two pre-specified secondary endpoints. The endpoints were the proportion of subjects with eradication of *Demodex* mites at Day 43 and the proportion of subjects achieving a composite cure (collarette and erythema Scores = 0) in the upper eyelid of at Day 43.

The statistical analysis plan for TRS-010 (SATURN-2) allowed for evaluation of the three prespecified secondary endpoints using the Hochberg procedure. The secondary endpoint evaluation shows that lotilaner ophthalmic solution demonstrates statistical significance over vehicle for eradication of mites, erythema cure and the composite score of collarette elimination with cure of erythema.

Primary Efficacy Endpoints – Proportion of Subjects Achieving 2 or less lashes with collarettes on the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	SATURN-1		SATURN-2	
	Lotilaner N = 212	**Vehicle N = 209**	**Lotilaner N=203**	**Vehicle N=209**
2 or less lashes with collarettes, N (%) (SE)	92 (43%)	15 (7%)	108 (53%)	25 (12%)
Difference in proportion cured p-value[b]	36%, p< 0.001		41%, p< 0.001	

Discontinuation of study drug and/or nonoptimal compliance were ignored. Missing data due to subject discontinuation specifically from lack of efficacy or adverse events were imputed as failures. Missing data due to all other reasons were imputed using multiple imputation with the randomized study drug-based Markov Chain Monte Carlo methodology. The multiple imputation datasets were used to calculate cure based on a collarette score of 0 at Day 43. Source: Table 14.2.2.1.1 Saturn-1 CSR
[a] The difference was computed as Lotilaner minus vehicle.
[b] The p-value was from a difference of proportions test.

Secondary Efficacy Endpoints – Proportion of Subjects with Eradication of *Demodex* Mites in the Analysis Eye at Day 43 and Proportion of Subjects Achieving a Composite (Collarette and Erythema Scores = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set) and Erythema Cure

	Saturn 1		Saturn 2	
	Lotilaner	**Vehicle**	**Lotilaner**	**Vehicle**
Eradication of *Demodex* mites	N=212	N=209	N=203	N=209
Cured (mite density = 0), (%)	142 (67)%	36 (17)%	100 (49%)	29 (14%)
Difference in proportion of mites cured p-value[b]	50%, p< 0.001		36%, p< 0.001	
Composite (collarette and erythema scores), (%)	29 (14%)	2 (1%)	37 (18%)	8 (3%)
Difference in composite proportion, p-value[b]	13%, p<0.001		15%, p<0.001	
Erythema Cure (erythema score = 0), %	40 (19%)	14 (7%)	60 (30%)	18 (9%)
Difference in proportion cured, p-value[b]	12%, p<0.001		21%, p<0.001	

Discontinuation of study drug and/or nonoptimal compliance were ignored. Missing data due to subject discontinuation specifically from lack of efficacy or adverse events were imputed as failures. Missing data due to all other reasons were imputed using multiple imputation with the randomized study drug-based Markov Chain Monte Carlo methodology. Multiple imputation datasets were used to calculate cure at Day 43 using a 1-sided alpha of 0.025. Source: Table 14.2.3.1.1 and Table 14.2.4.1.1 Saturn-1 CSR
[a] The difference was computed as Lotilaner minus vehicle.
[b] The p-value was from a difference of proportions test.

Sensitivity analyses were used to evaluate the robustness of the secondary efficacy analyses. In these analyses, missing data for all secondary endpoints was imputed as failures. The results of each sensitivity endpoint analysis were similar to the results for the same endpoint in the primary analysis.

Reviewer's Comments: *All primary and secondary endpoints were statistically significant.*

Subpopulations
Efficacy results were analyzed by gender, age, race and ethnicity. Since most subjects in the combined population were White (89%) and most were not Hispanic or Latino (93%), definitive conclusions regarding results in the subgroups of race and ethnicity could not be drawn. Nevertheless, no meaningful trends were observed in any subgroup that would suggest a difference in efficacy for Lotilaner based solely on the intrinsic factors of age, sex, race, ethnicity, or iris color.

Safety

Safety Database

Saturn-1 and Saturn-2 studies combined, 1540 subjects were screened and 833 were randomized to study drug, including 415 in the lotilaner ophthalmic solution group and 418 in the vehicle group. Overall, 806 of 833 randomized subjects (97%) completed the studies through the Day 43 visit. The percentages of subjects who completed the Day 43 visit were similar in the lotilaner ophthalmic solution and vehicle groups and also in each of the studies.

Studies Saturn-1 and Saturn-2: Subject Disposition (All Randomized Subjects)

	Saturn-1		Saturn-2	
	Lotilaner	**Vehicle**	**Lotilaner**	**Vehicle**
Randomized	212	209	203	209
Completed Treatment Interval (Day 43 Visit), n (%)[a]				
Yes	209 (98.6%)	204 (97.6%)	193 (95.1%)	200 (95.7%)
No	3 (1.4%)	5 (2.4%)	10 (4.9%)	9 (4.3%)
Completed Day 57 visit[b]				
N	69	65	131	134
Yes	68 (98.6%)	64 (98.5%)	122 (93.1%)	125 (93.3%)
No	1 (1.4%)	1 (1.5%)	9 (6.9%)	9 (6.7%)

Note: All subjects in both studies who did not discontinue early had a Day 43 visit; subjects in Cohort 2 of Study Saturn-1 and subjects in Cohort 1 of Study Saturn-2 who did not discontinue early also had a Day 57 visit.
[a] Percentages were based on the total number of randomized subjects. Subjects whose last visit was recorded as the Day 43 visit or later were counted as having completed the Day 43 visit. All other subjects were counted as not having completed the Day 43 visit.
[b] Percentages were based on the total number of subjects in Study Saturn-1 Cohort 2 and Study Saturn-2 Cohort 1. Subjects whose last visit was recorded as the Day 57 visit or later were counted as having completed the Day 57 visit. All other subjects in Saturn-1 Cohort 2 or Saturn-2 Cohort 1 were counted as not having completed the Day 57 visit.
Source: ISS, Table 1.1; Saturn-1 CSR, Section 7.1; Saturn-2 CSR, Section 7.1

Reviewer's comments:
There was adequate exposure for this indication.

Deaths
No deaths occurred in the two pivotal studies included in the clinical development program for lotilaner ophthalmic solution in the treatment of Demodex blepharitis.

Serious Adverse Events for Studies Saturn-1 and Saturn-2:
Treatment-Emergent Serious Adverse Events (Safety Analysis Set)

Preferred term	Lotilaner, N= 415 n (%)	Vehicle N=418 n (%)
Diabetic retinopathy	1 (0.2)	0
Gastrointestinal hemorrhage	1 (0.2)	0
Intestinal obstruction	1 (0.2)	0
COVID-19	1 (0.2)	0
Pneumonia	1 (0.2)	0
Vascular access site pseudoaneurysm	0	1 (0.2)
Bladder cancer	0	1 (0.2)
Hematuria	1 (0.2)	0
Uterine prolapse	1 (0.2)	0
Dyspnea	0	1 (0.2)

Summary of Clinical Safety Table 10.
COVID-19 = coronavirus disease 2019
All events were coded using the Medical Dictionary for Regulatory Activities, version 23.0.
Source: ISS, Table 4.2.7

No adverse safety signals or trends were observed based on a review of SAEs and other significant TEAEs.

Treatment-Emergent Ocular Events Occurring in ≥ 1% of Subjects in Either Study Drug Group by Preferred Term (Safety Analysis Set), Saturn-1 and Saturn-2

System organ class- Preferred term	Lotilaner N =415 n (%)	Vehicle N = 418 n (%)
Eye disorders	51 (12%)	44 (10%)
Instillation site pain	41 (10%)	30 (7%)
Visual acuity reduced	11 (3%)	11 (3%)
Chalazion/Hordeolum	7 (2%)	4 (1%)
Instillation site pruritus	4 (1%)	8 (2%)
Eye pain	4 (1%)	3 (1%)
Dry eye	4 (1%)	3 (1%)
Punctate keratitis	4 (1%)	1 (0.2%)

The table includes only Preferred Terms (PTs) that were reported for ≥ 1% of the subjects in either study drug group; SOCs were omitted if no individual PT within that SOC occurred in ≥ 1% of the subjects in either study drug group. Subjects who experienced more than 1 treatment-emergent adverse event within a given SOC or PT were counted once within that SOC or PT.
Source: ISS, Table 4.2.1.1 and Summary of Clinical Safety Table 6

There were no non-ocular TEAEs that occurred in ≥ 1% of subjects in either study.

The rate of adverse events that occurred in the trials was low with most occurring at a rate of no greater than 1%. In addition, the rate of adverse events was similar between lotilaner ophthalmic solution and vehicle. The events that occurred at a higher incidence include Instillation site pain (10%), Chalazion/Hordeolum (2%) and Punctate keratitis (1%).

Biomicroscopy and Fundus Exam
There were no clinically relevant changes in the fundus exam that occurred in either treatment group during the clinical trials. Biomicroscopy was conducted at selected study sites to measure endothelial cell density. See endothelial cell density (ECD) below.

QT
The Interdisciplinary Review Team for Cardiac Safety Studies completed a QT study review on 12/1/22. No significant QTcF prolongation effect of lotilaner was detected in this QTc assessment of data collected in Study TRS-013.

Endothelial Cell Density
The applicant responded on June 21, 2023, to an information request regarding Endothelial Cell Density data from Study Saturn-2.

Percent Change from Baseline in Endothelial Cell Density at Day 90

	Right Eye		Left Eye	
Percent Change	**Lotilaner** (n=153)	**Vehicle** (n=152)	**Lotilaner** (n=154)	**Vehicle** (n=153)
≥ 50% Loss	0	0	0	0
≥ 40% and < 50% Loss	1 (0.7%)	1 (0.7%)	0	0
≥ 30% and < 40% Loss	0	0	0	0
≥ 20% and < 30% Loss	1 (0.7%)	0	1 (0.7%)	0
≥ 10% and < 20% Loss	4 (3%)	1 (0.7%)	5 (3%)	0
< 10% Change	138 (90%)	141 (93%)	138 (90%)	143 (94%)
≥ 10% and < 20% Increase	6 (4%)	3 (2%)	7 (5%)	4 (3%)
≥ 20% and < 30% Increase	3 (2%)	3 (2%)	1 (0.7%)	1 (0.7%)
≥ 30% and < 40% Increase	0	1 (0.7%)	0	1 (0.7%)
≥ 40% and < 50% Increase	0	1 (0.7%)	0	1 (0.7%)
≥ 50% Increase	0	1 (0.7%)	2 (1.3%)	3 (2%)

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The submitted data is an adequate evaluation of the potential effect of lotilaner on corneal endothelial cell density. The Agency will not be requesting a PMR for additional evaluation endothelial cell density data.

Advisory Committee Meeting

There were no issues raised during the review of this application that were thought to benefit from an Advisory Committee meeting.

Pediatrics

An initial pediatric study plan (iPSP) was filed in March 2022, and iPSP agreement was received on May 31, 2022. The iPSP requested a full product specific waiver for all pediatric age groups (i.e., birth to < 18 years) on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients. Demodex blepharitis is rare in the pediatric population.

The application was present at PeRC on March 21, 2023. The Division and PeRC agreed with the plan to request full waiver for all pediatrics because necessary studies are impossible or highly impracticable because the condition rarely occurs in the pediatric population.

BIOSTATISTICS

From the Statistical Review finalized on 4/7/2023:

Efficacy Results

Study SATURN-1

The statistical reviewer verified the results of the sponsor for the primary endpoint as well as for the secondary endpoints, using the method (MCMC) proposed for dealing with missing data. Since the assumptions for applying the multiple imputation based on MCMC methodology were difficult to verify, the statistical reviewer's efficacy analyses were based on all randomized patients (FAS population) by viewing the treatment discontinuation by Day 43 (missing outcomes at Day 43) as treatment failure.

Sensitivity Analyses

The Statistical Reviewer carried out sensitivity analyses on the primary and secondary endpoints by viewing missing data as treatment failure based on the change of (Day 43 outcome – baseline) (i.e., set change=0 for missing data) using two sample t-tests at a significance level of 0.05 (2-sided). These analyses were carried out on the collarette, the composite, and erythema grading cure score=0, and Mite Density from the analysis eye. The results of all sensitivity analyses are significant at a level of 0.05 (2-sided), supporting the findings in the primary analysis.

Sensitivity Analysis of Mean Scores for Primary and Secondary Endpoints. All Missing Data Were Imputed as Treatment Failures (FAS Population)

Endpoint	Lotilaner N=212	Vehicle N=209	Difference
	Mean (SE)	Mean (SE)	Mean diff (SE) (p-value*)
Collarette (Upper Eyelid) score=0	-1.96 (0.08)	-0.57 (0.07)	-1.39 (0.10) (<.0001)
Composite Cure (Upper Eyelid)	-2.38 (0.11)	-0.75 (0.09)	-1.63 (0.14) (<.0001)
Erythema Scores (Upper Eyelid)[&]	-0.44 (0.05)	-0.22 (0.05)	-0.22 (0.07) (0.0011)
Mite Density	-2.98 (0.12)	-1.74 (0.13)	-1.23 (0.17) (<.0001)

* Two sample t-test.
[&] N=211 for **Lotilaner**, n=208 for Vehicle

Subgroup Summaries

Since the randomization of subjects in this study was not stratified by subgroup categories, such as age, gender, race etc., statistical analysis of subgroups based on hypothesis tests are not carried out. Therefore, the statistical reviewer verified the sponsor's descriptive subgroup analysis of subjects achieving a cure at Day 43 for the subgroups of sex, age category (< 65 and ≥ 65 years), and race. The analyses were performed using observed data in the FAS, supporting a greater treatment effect for Lotilaner relative to that for vehicle in subgroups with reasonable sample sizes.

Study SATURN-2

Sensitivity Analyses

The Statistical Reviewer carried out sensitivity analyses on the primary and secondary endpoints by viewing missing data as treatment failure for the treatment effect based on the change of (Day 43 outcome – baseline) (i.e., set change=0 for missing data) using two sample t-tests at a significance level of 0.05 (2-sided). These analyses were carried out on the collarette, the composite, and erythema grading cure score=0, and Mite Density from the analysis eye. The results of all sensitivity analyses are significant at a level of 0.05 (2-sided), supporting the findings in the primary analysis.

Sensitivity Analysis of Mean Scores for Primary and Secondary Endpoints. All missing data were imputed as failures (FAS Population)

Endpoint	LOTILANER N=203	Vehicle N=209	Difference
	Mean (SE)	Mean (SE)	Mean diff (SE) (p-value*)
Collarette (Upper Eyelid) score=0	-2.06 (0.11)	-0.86 (0.09)	-1.20 (0.14) (<.0001)
Composite Cure (Upper Eyelid)	-2.53 (0.15)	-1.09 (0.13)	-1.44 (0.20) (<.0001)
Erythema Scores (Upper Eyelid)	-0.47 (0.07)	-0.23 (0.06)	-0.24 (0.09) (0.0086)
Mite Density	-2.56 (0.14)	-1.73 (0.15)	-0.83 (0.20) (<.0001)

* Two sample t-test.

Subgroup Summaries

In Study TRS-090, the randomization of subjects was not stratified by subgroup categories, such as age, gender, race etc., statistical analysis of subgroups based on hypothesis tests are not carried out. Therefore, this reviewer verified the sponsor's descriptive subgroup analysis of subjects achieving a cure at Day 43 for the subgroups of sex, age category (< 65 and ≥ 65 years), and race (White and non-White). The analyses were performed using observed data in the FAS, suggesting a greater treatment effect of LOTILANER relative to that of vehicle in subgroups consistently.

Collective evidence

Collective evidence to support the efficacy and safety of Lotilaner relative to vehicle for the treatment of *Demodex* blepharitis for 43 days were based on data from two pivotal studies, TRS-009 (SATURN-1) and TRS-010 (SATURN-2). All the descriptive analysis, primary analysis, sensitivity analysis, and subgroup analysis provided consistent results for supporting the efficacy of Lotilaner in the treatment of Demodex.

Conclusions and Recommendations

Overall, the statistical reviewer concluded that the data of the two pivotal studies provided substantial evidence for Lotilaner efficacy benefit, applied twice daily (morning and evening) in each eye for 43 days, in the treatment of *Demodex* blepharitis.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators in the original NDA submission.

Covered Clinical Studies [TRS-009 (Saturn-1) and TRS-010 (Saturn-2)]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Patient Experience Data

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

	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☒ Observer reported outcome (ObsRO)	Clinical/Biostat*
	☒ Clinician reported outcome (ClinRO)	Clinical/Biostat*
	☐ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	

	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
□	Patient experience data was not submitted as part of this application.			

** Drop comfort was assessed at every study visit through Day 43 in both studies using a 5-point categorial scale with anchors of "very comfortable" and "very uncomfortable"; however, the results could not be used since the assessments occurred after the eye had been anesthetized.*

Office of Scientific Investigations (OSI)

From the OSI Clinical Inspections Summary dated April 28, 2023:

The clinical sites of Drs. Meyer, Paauw, Vollmer, and Schechter were inspected in support of this NDA. At Dr. Schechter's site, four subjects, although not eligible for the study, were enrolled, randomized, and dosed. This protocol deviation was reported to the FDA. Otherwise, Studies Saturn-1 and Saturn-2 appear to have been conducted adequately and the data generated by the inspected sites appear acceptable in support of the respective indication.

OPDP and DMEPA

The Division of Medication Error Prevention and Analysis 1 (DMEPA) completed a review dated January 17, 2023. Revisions were proposed for the draft prescribing information (PI), professional sample and trade container labels and carton labeling.

The Office of Prescription Drug Promotion (OPDP)completed a review of the package insert and carton/ container labeling on June 20, 2023. They had no additional suggested revisions to the revised draft labeling.

Post-marking Risk Management

There are no proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

Regulatory Action

NDA 217603 Xdemvy (lotilaner ophthalmic solution) 0.25% will be approved for the treatment of Demodex blepharitis.

Labeling

Attached is the agreed-upon labeling for NDA 217603 Xdemvy (lotilaner ophthalmic solution) 0.25% for the treatment of Demodex blepharitis.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

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