CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217603Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW 217603

Application Type	NDA
Application Number(s)	NDA 217603 (IND 143686)
Priority or Standard	S
Submit Date(s)	August 25, 2022
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PDUFA Goal Date	June 23, 2023
Division/Office	OSM/DO
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	December 15, 2022
Established/Proper Name	lotilaner ophthalmic solution 0.25%
(Proposed) Trade Name	Xdemvy
Applicant	Tarsus Pharmaceuticals, Inc.
Dosage Form(s)	Topical ocular
Applicant Proposed Dosing Regimen(s)	Twice daily in (b) (4) for 6 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of demodex blepharitis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with demodex blepharitis

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TP-03	lotilaner ophthalmic solution

1. Executive Summary

1.1. Product Introduction

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).

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 217603 for lotilaner ophthalmic solution, 0.25% is recommended for approval for the treatment of demodex blepharitis. Two trials (TRS-009 and TRS-010) were submitted with this NDA to support the approval of lotilaner.

Endpoints for this indication should ensure that the symptoms associated with demodex blepharitis have been completely resolved. The endpoints that can show a clinically relevant benefit include complete resolution of eyelash collarettes, eradication of eyelash mites, and resolution of eyelid erythema.

TRS 009 (Saturn-1) demonstrated efficacy of lotilaner ophthalmic solution by showing complete resolution of eyelash collarettes for the primary endpoint in addition to the secondary endpoints of mite eradication and composite score (collarettes and eyelid erythema). TRS-010 (Saturn-2), demonstrated efficacy by showing complete resolution of eyelash collarettes for the primary endpoint in addition to the secondary endpoints of mite eradication, erythema and composite score (collarettes and eyelid erythema).

The results of these clinical trials support the use of lotilaner ophthalmic solution, 0.25% for the treatment of demodex blepharitis.

1.3. Benefit-Risk Integrated Assessment

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

The overall exposure to lotilaner ophthalmic solution dosed twice per day for at least 4 weeks was 726 subjects throughout the development program. In the phase 3 trails, 415 subjects were treated with the to-be-marketed lotilaner ophthalmic solution, 0.25%. 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%) and reduced visual acuity (3%). 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 an approved drug product for the treatment of demodex blepharitis.
Benefit	Demonstrating a complete resolution of symptoms of demodex blepharitis (e.g., eyelash collarettes and eyelid erythema) in demodex blepharitis patients provides a clinically relevant benefit.	TRS 009 (Saturn-1) a multicenter, randomized, adequate and well-controlled clinical study demonstrated efficacy by showing complete resolution of eyelash collarettes, mite eradication and composite score (collarettes and eyelid erythema) with lotilaner. TRS-010 (Saturn-2), a multicenter, randomized, adequate and well-controlled clinical study demonstrated efficacy by showing complete resolution of eyelash collarettes, mite eradication, erythema and composite score (collarettes and eyelid erythema) with lotilaner.
Risk and Risk Management	The events that occurred at a higher incidence with lotilaner compared to the vehicle group include instillation site pain, hordeolum and punctate keratitis.	Treatment with lotilaner for the treatment of demodex blepharitis has an acceptable risk-benefit profile.

1.4. 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)	**See reviewer comment*
		☒	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

** 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.*

2. Therapeutic Context

2.1. Analysis of Condition

Blepharitis is a disease characterized by inflammation of the eyelid margins. Subjects with blepharitis often experience red and watery eyes, burning or stinging in the eyes, itchy, red, and/or swollen eyelids, and a crustiness around the eyelashes; blepharitis can also lead to abnormal growth or loss of eyelashes. In the United States (US), blepharitis is estimated to affect as many as 19 million people. Blepharitis is commonly associated with infestation of eyelash follicles and meibomian glands by two species of microscopic parasitic mites: *Demodex folliculorum* or *Demodex brevis*.

2.2. Analysis of Current Treatment Options

The are no pharmaceutical products currently approved to treat demodex blepharitis.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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) and has been shown to be effective against Demodex mites in dogs (Snyder 2017). 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 as a veterinary medicine to treat flea and tick infestations in dogs and cats in the European Union (Credelio EMA Approval 2017).

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-IND meeting was held with Tarsus on 04 June 2019. The following issues were discussed:

- Study design of Study TRS-009:
  - 6-week treatment duration of TP-03 (lotilaner), twice daily
  - Eligibility criteria
  - Primary endpoint of collarette cure (based on a score of 0 meaning the presence of 2 or less lashes with collarettes on the upper eyelid of the analysis eye)
  - Secondary endpoint of mite eradication (0 mites/lash for the analysis eye)
  - Secondary endpoint of composite cure (collarette cure and a score of 0 for lid erythema)
- The need to include dilated fundus examinations at baseline and the end of study in at least one of the studies
  - The minimum number of subjects (300) to be treated with the final formulation of lotilaner ophthalmic solution

The IND (143686) was filed by Tarsus on 24 July 2020. The applicant provided the following points of clarification in response to Agency's information request:

- Specified in the protocol that the definition of mite eradication is a mite density of 0.
- Committed to assess PK using the to-be marketed formulation of lotilaner ophthalmic solution
- Committed to optimize the sampling plan to adequately characterize the full PK of lotilaner ophthalmic solution
- Committed to revise the primary and secondary efficacy analyses, as well as the associated sensitivity analyses, in the statistical analysis plan in accordance with FDA recommendations

A Type C meeting held on 08 December 2020:

- The applicant did not plan to conduct dilated fundus examinations in Study TRS-010 pending results from Study TRS-009.
- Endothelial cell counting was to be performed at baseline, Week 6, and Month 3 in Study TRS-010. Data from the 3-month endothelial cell count assessments would be provided in the 120-day safety update.
  Up to 50% of the same study centers could be used in both studies, with the understanding that each study would enroll unique subjects (i.e., the same subject could not participate in both pivotal studies).

3.3. Foreign Regulatory Actions and Marketing History

Lotilaner ophthalmic solution has not been approved for marketing in any country.

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

4.1. Office of Scientific Investigations (OSI)

The results of inspections are not available at the time of this review. Results will be addressed in the CDTL review.

4.2. Product Quality

Lotilaner Ophthalmic Solution, 0.25% is a sterile, preserved, multi-dose ophthalmic solution containing lotilaner, 0.25%, as the active ingredient. It is preserved with potassium sorbate and contains the following additional inactive ingredients: Edetate disodium, Hypromellose (HPMC (b) (4)), Polyoxyl 35 castor oil ((b) (4)), Glycerin, Dibasic sodium phosphate, Monobasic sodium phosphate, and Water for Injection. Lotilaner Ophthalmic Solution, 0.25% is a drug-led combination product comprised of a drug constituent and a device constituent part. The device constituent (i.e., container-closure system (CCS)) of the Lotilaner Ophthalmic Solution, 0.25% drug product includes the bottle, tip, and cap.

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	Preservative	(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)

4.3. Clinical Microbiology

See Clinical Microbiology Review

4.4. Nonclinical Pharmacology/Toxicology

Lotilaner is a member of the isoxazoline family of compounds. Isoxazolines are inhibitors of insect and acarine GABA mediated chloride channels. The GABA mediated chloride influx leads to hyperpolarization of the cellular membrane and generates an inhibitory postsynaptic potential, which decreases the probability of an action potential. 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.

4.5. Clinical Pharmacology

Study TRS-012 was designed to evaluate the systemic whole blood PK of lotilaner following topical ophthalmic single and repeat doses of lotilaner ophthalmic solution in healthy adult subjects for 42 days. This was a single-center, open-label, single-arm study.

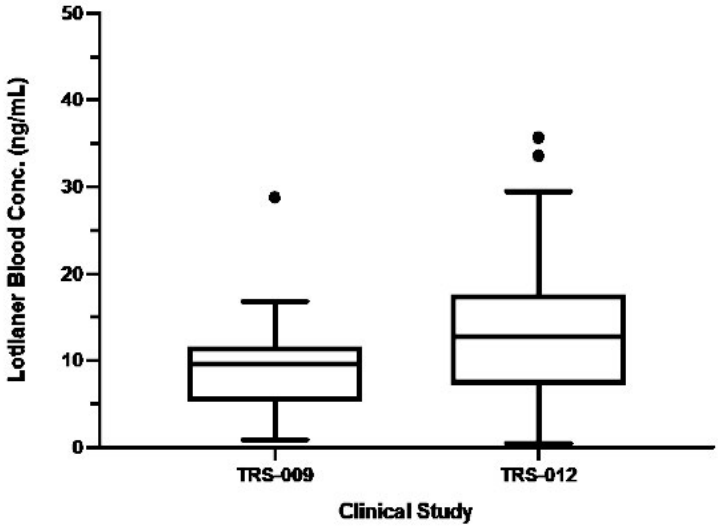
Study TRS-012: Summary Statistics of Whole Blood Lotilaner Pharmacokinetic Parameters Following Single and Repeat Topical Ocular Dose Administration of TP-03 in Healthy Subjects (PK Analysis Population)

Parameter	T_{max} (h) N = 24	C_{max} (ng/mL) N = 24	$AUC_{0-\tau}$[a] (h•ng/mL) N = 24	AUC_{0-24} (h•ng/mL) N = 24	AUC_{0-t} (h•ng/mL) N = 24	T_{half} (h) N= 21	$T_{half,eff}$ (h) N = 18
Day 1	2.00 (1.00-8.05)	0.596 (52%)	5.75[b] (48.5%)	9.98[c] (49%)	6.44 (96%)	NC	NC
Day 42	1.00 (0.00-334)	17.8 (53%)	149 (52%)	293 (54%)	20600 (55%)	1400 (70.5%)	264 (47%)

NC = not calculated
All parameters are reported as arithmetic mean (CV%), except Tmax, which is reported as median (range).
[a] AUC0-τ corresponds to the AUC0-12 for Day 1 where τ is the dosing interval of 12 hours.
[b] N = 18.
[c] N = 17.
Source: TRS-012, Table 14.2.1.2.1 and Table 14.2.2.2.1

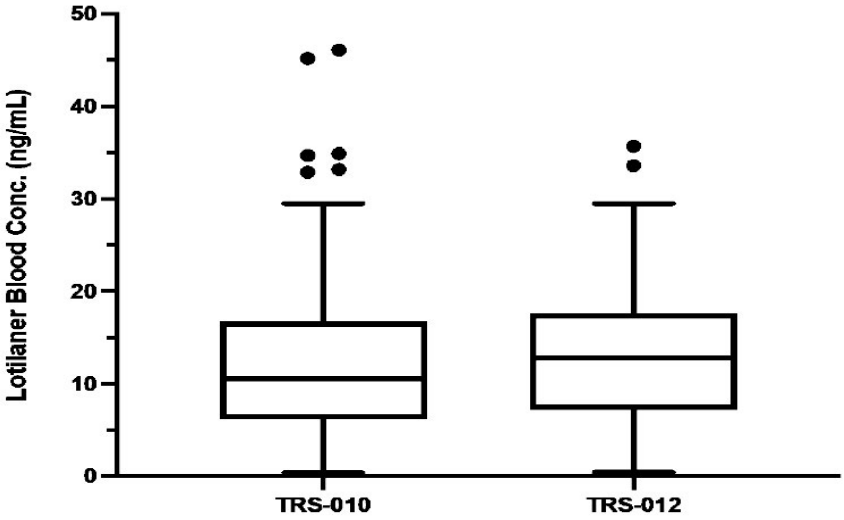
Forty-one subjects in TRS-009 (Saturn-1) and 327 subjects in TRS-010 (Saturn-2) had blood samples were collected at the end of treatment to determine the concentration of lotilaner in whole blood. Subjects had blood drawn on Day 42 without controlling for when the last eye drop was administered.

Studies TRS-009 and TRS-012: Box Plot of Lotilaner Blood Concentration at Day 42



Conc = concentration
Tukey box and whiskers plot: solid line within the box represents the median value; the box represents the interquartile range; whiskers are 1.5 × interquartile range; filled circles represent outliner data. Source: Summary of Clinical Pharmacology Fig. 4

Studies TRS-010 and TRS-012: Box Plot of Lotilaner Blood Concentration at Day 42



Conc = concentration
Tukey box and whiskers plot: solid line within the box represents the median value; the box represents the interquartile range; whiskers are 1.5 × interquartile range; filled circles represent outliner data. Source: Summary of Clinical Pharmacology Fig. 5

The mean concentration after treatment is similar between the studies. The systemic exposure at the end of treatment in subjects with Demodex blepharitis does not appear to be different from the systemic exposure in healthy volunteers.

4.6. Devices and Companion Diagnostic Issues

Lotilaner Ophthalmic Solution, 0.25% is a drug-led combination product comprised of a drug constituent and a device constituent part. The device constituent (i.e., container-closure system (CCS)) of the Lotilaner Ophthalmic Solution, 0.25% drug product includes the bottle, tip, and cap.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Identifier	Title of the Study	Objective(s) of the Study	Study Design; Study Centers	Study Drug(s): Route of Administration and Regimen	Enrollment (Treated / Completed)	Subject Population
Pivotal Studies						
TRS-009 (Saturn-1) Phase 2b/3	Randomized, Controlled, Multicenter, Double-Masked, Parallel, Phase 2b/3 Trial to Evaluate the Safety and Efficacy of TP-03 for the Treatment of *Demodex* Blepharitis (Saturn-1)	Evaluate the efficacy of TP-03, as determined by collarette score, mite eradication, and a composite of the collarette and erythema scores Evaluate the safety of TP-03	Randomized, double-masked, safety, efficacy, and systemic lotilaner concentration study 15 study centers in the United States	TP-03 or Vehicle: one topical ocular drop instilled in each eye twice daily for 43 days	421/411 TP-03: 212/208 Vehicle: 209/203	Subjects with *Demodex* blepharitis
TRS-010 (Saturn-2) Phase 3	Randomized, Controlled, Multicenter, Double-Masked, Parallel, Phase 3 Trial to Evaluate the Safety and Efficacy of TP-03 for the Treatment of *Demodex* Blepharitis (Saturn-2)	Evaluate the efficacy of TP-03, as determined by collarette score, mite eradication, erythema score, and a composite of the collarette and erythema scores Evaluate the safety of TP-03	Randomized, double-masked, safety, efficacy, and systemic lotilaner concentration study 21 study centers in the United States	TP-03 or Vehicle: one topical ocular drop instilled in each eye twice daily for 43 days	412/393 TP-03: 203/193 Vehicle: 209/200	Subjects with *Demodex* blepharitis
Pharmacokinetic Study						
TRS-012 (Hyperion) Phase 1	Pharmacokinetic Study to Evaluate the Whole Blood Pharmacokinetics of TP-03 Following Six Week Topical Ocular Administration	Evaluate the systemic lotilaner pharmacokinetics of single and multiple applications of TP-03 Evaluate the safety of TP-03	Single arm, open-label, pharmacokinetic and safety study 1 study center in Canada	TP-03: one topical ocular drop instilled in each eye once or twice daily for 42 days	24/24 (all TP-03)	Healthy subjects

Source: section 2.5 Clinical Overview page 8

5.2. Review Strategy

The primary evidence of safety and efficacy to support lotilaner ophthalmic solution for the treatment of demodex blepharitis was based on data from two (2) of the trials TRS-009 (Saturn-1) and TRS-010 (Saturn-2) which evaluated efficacy endpoints that are considered clinically meaningful by the Division. Treatment is expected to remove all of the cylindrical dandruff (collarettes) found at the base of the lashes and eradicate the mites themselves. Endpoints for demodex blepharitis that were used to evaluate the efficacy of lotilaner ophthalmic solution include:

- *Collarette grade = 0*
- *Mite eradication*

- *Lid erythema = 0*

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. TRS-009 (Saturn-1)

6.1.1. Study Design

Overview and Objective

The primary objective was to demonstrate the safety and efficacy of lotilaner ophthalmic solution as a treatment for *Demodex* blepharitis. The secondary objectives were to demonstrate the efficacy of lotilaner ophthalmic solution in the eradication of *Demodex* mites from the eyelid margin, and to demonstrate the efficacy of lotilaner ophthalmic solution in the elimination of collarettes and erythema from the eyelid margin. The tertiary objective was to demonstrate the efficacy of lotilaner ophthalmic solution in the reduction from baseline of the mean collarette score and the mean mite density on the upper eyelid of the analysis eye at each follow-up visit.

Trial Design

This was a randomized, controlled, multicenter, double-masked, parallel group, Phase 2b/3 study designed to evaluate the safety and efficacy of lotilaner ophthalmic solution in the treatment of *Demodex* blepharitis. Up to approximately 418 adult (≥ 18 years) subjects with *Demodex* blepharitis were to be enrolled. Subjects were randomized (1:1) to receive either lotilaner ophthalmic solution or vehicle. The study drugs were masked with subjects instructed to instill a single drop of the assigned study drug twice daily (morning and evening) in each eye. The study drug administration period was 43 days (approximately 6 weeks).

The study was extended in protocol amendment version 3.0. Subjects who were already enrolled at the time of or enrolled following implementation of protocol version 3.0, also attended a follow-up on Day 57. Subjects who completed the study prior to implementation of protocol version 3.0 were classified as being in Cohort 1, with Day 43 representing their last study visit; all other subjects were classified as being in Cohort 2 and were to have completed the study on Day 57.

At selected study centers, subjects may also have had specular microscopy examinations, provided whole blood for drug concentration assessments, and/or had photographs taken of their eyelids.

Study TRS-009: Schedule of Assessments

Procedures	Screening Day −14 to 1	Enrollment/ Study Drug Initiation Day 1	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 −3/+4 days	Day 43 −3/+7 days	Day 57 −6/+14 days
Informed consent	X						
Demographics	X						
Medical/ophthalmic history	X						

Concomitant medication review	X	X	X	X	X	X	X
Drop comfort		X	X	X	X	X	
Corrected distance visual acuity	X	X[a]	X	X	X	X	X
Slit-lamp biomicroscopy	X	X[a]	X	X	X	X	X
Collarette and eyelid margin erythema grading	X		X	X	X	X	X
Corneal fluorescein staining		X	X	X	X	X	X
Intraocular pressure		X				X	X
Demodex count	X			X	X	X	X
Specular microscopy (at selected study centers)		X				X	
Dilated fundus examination		X				X	
Eyelid photos (at selected study centers)		X				X	X
Blood sample collection (at selected study centers)						X	
Urine pregnancy test[b]	X					X	
Randomization		X					
Dispense study drug; diary		X					
Collection and review of subject diary			X	X	X		
Adverse event review and evaluation		X	X	X	X	X	X
Collect study drug; diary						X	
End of study drug assessments						X	
Observational study assessment (Cohort 2 only)							X
Study exit						X[c]	X[d]

[a] If the screening and Day 1 visits were completed on the same day, this procedure did not have to be repeated.
[b] Female subjects of childbearing potential only.
[c] For subjects in Cohort 1.
[d] For subjects in Cohort 2.
Source: CSR TRS-009 table 2

Diagnosis and Main Criteria for Inclusion:

Eligible subjects included adults (≥ 18 years) with each of the following in at least 1 eye: > 10 lashes with collarettes present on the upper eyelid (collarette score ≥ 2); at least mild erythema of the upper eyelid margin; and a *Demodex* density, upper and lower eyelids combined, of ≥ 1.5 mites per lash. Eligible subjects must also have had a corrected distance visual acuity (CDVA) better than or equal to +0.7 logMAR in each eye, assessed with the Early Treatment Diabetic Retinopathy Study chart.

Study TRS-009: Collarette Grading Scale

Score	Clinical Interpretation
0	0 to 2 lashes have collarettes per eyelid
1	3 to 10 lashes have collarettes per eyelid
2	More than 10 but less than 1/3 of lashes have collarettes per eyelid
3	1/3 or more but less than 2/3 of lashes have collarettes per eyelid
4	2/3 or more of lashes have collarettes per eyelid

For collarette grading, half-unit increments were not allowed.

Study TRS-009: Eyelid Margin Erythema Grading Scale

Score	Severity	Clinical Interpretation
0	Normal	Normal age-related lid coloration
1	Mild	Pink capillary involvement along the lid edge, no patches of confluent capillary redness throughout the lid edge
2	Moderate	Deep pink or red confluent capillary redness present locally along the lid edge
3	Severe	Deep red, diffuse confluent capillary redness present along the lid edge

For eyelid margin erythema grading, half-unit increments were not allowed.

Administered drug and placebo
Lotilaner Ophthalmic Solution, 0.25% - Lot number: 182130 (LTL001)

Vehicle (i.e., the same formulation as lotilaner ophthalmic solution but without the active pharmaceutical ingredient) - Lot number: 182129 (LTL001)

Duration of Treatment:
43 days (approximately 6 weeks)

Study Endpoints

Efficacy:
Primary efficacy endpoint:

- Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43

Secondary efficacy endpoints:

- Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Day 43
- Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred to as a composite cure)

Safety:

- Assessment of treatment-related, treatment-emergent adverse events (TEAEs)
- CDVA testing
- IOP measurements
- Slit-lamp biomicroscopy examinations
- Dilated fundus examinations
- Corneal fluorescein staining results
- Specular microscopy (conducted at 2 study centers)

Statistical Analysis Plan

Descriptive statistics were used to provide an overview of the efficacy and safety results. Categorical variables (i.e., discrete variables) were summarized by frequency counts and percentages for each response category, while continuous and ordinal variables were summarized using the sample size, mean, standard deviation (SD), median, minimum, and maximum values for the data collected at each applicable visit. Where inferential testing was conducted, unless otherwise stated, the statistical tests were 1-sided with an alpha level of 0.025. Confidence intervals (CIs) for the differences between study drug groups, as well as changes from baseline, were 2-sided at 95% confidence.

Results for the primary and secondary efficacy endpoints were presented by study drug group using descriptive statistics. In these analyses, comparisons between study drug groups were performed using a difference of proportions test.

A closed hierarchical testing structure was used where the analysis was performed for the primary efficacy endpoint and, only if successful, was performed for the secondary efficacy endpoints using the Hochberg testing strategy.

Four analysis sets were defined for this study: the full analysis set (FAS), the per protocol (PP) analysis set, the COVID-19 analysis set, and the safety analysis set.

Full Analysis Set: all randomized subjects.
Per Protocol Analysis Set: subjects (and their visits) who did not have a protocol deviation

COVID-19 Analysis Set:	all randomized subjects with the exception of those who discontinued the study due to COVID-19 complications, would have discontinued the study due to COVID-19 had they remained on study, or had substantial COVID-19 related protocol deviations.
Safety Analysis Set:	all randomized subjects who instilled study drug at least once.

Protocol Amendments

The original protocol was revised twice (on 01 October 2020 and 25 January 2021

Revision 1 (Protocol Version 2.0):

- Added, at selected study centers, procedures to conduct specular microscopy to assess endothelial cell density and to collect a blood sample for analysis of lotilaner drug concentration; added information specific to the methods and timing of the endothelial cell assessment procedure and the blood sample collection/analysis
- Added an allowance for subjects to be rescreened once if they failed to meet eligibility criteria and instructions to maintain their same screening number when rescreened
- Indicated that eyelid photography would be conducted only at selected study centers and added information specific to the methods for obtaining the eyelid photographs
- Revised the visit window at Day 22 to avoid overlap between visit windows at Day 15 and Day 22
- Added a definition of the analysis eye in the statistics section of the protocol
- Added clarifications to the inclusion and exclusion criteria (ie, changes that did not alter the criteria but made their intent clearer), along with minor language changes for clarity in the sections addressing lifestyle considerations, assessments of AEs and their reporting requirements, and confidentiality information

Revision 2 (Protocol Version 3.0):

- Added a Day 57 visit (i.e., a follow-up visit to be conducted 2 weeks after the last on-treatment study visit), along with the associated study procedures
- Clarified that subjects who would be expected to attend the Day 57 visit would be considered to comprise Cohort 2 of the study, while all other subjects would be considered to comprise Cohort 1
- Revised the study duration to address the addition of the Day 57 study visit
- Added tertiary efficacy endpoints to evaluate the existing endpoints through Day 57 for subjects in Cohort 2
- Clarified that the primary and secondary efficacy endpoints were to be evaluated at Day 43, and included time points for analyses of tertiary endpoints where they were not previously stated
- Clarified the procedures to be conducted at an unscheduled study visit
- Added that all statistical summaries and analyses would be performed for both cohorts combined unless specifically stated otherwise
- The SAP was approved on 26 May 2021, with an addendum issued on 29 March 2022. The final version and addendum of the SAP were in effect prior to database lock and breaking of the study drug mask. There were 3 notable differences between the analyses described in the approved SAP and the final revised version of the protocol. The differences between the SAP and the protocol were as follows:

- The primary, secondary, and tertiary endpoints were stated with less specificity in the protocol synopsis than in the protocol body and were each stated somewhat differently from the language used in the SAP to describe the same endpoint. The tertiary endpoints related only to Cohort 2 were inadvertently omitted from the protocol synopsis, were included in the body of the protocol, but lacked specificity that was provided in the SAP.
- The COVID-19 analysis set, which was defined in the SAP, was not included in the protocol
- The protocol stated the primary efficacy analysis would be based on a logistic regression; this was changed in the SAP, based on regulatory guidance indicating a preference for a difference of proportions test.

6.1.2. **Study Results**

Compliance with Good Clinical Practices

This study was conducted in accordance with the protocol and recognized standards including, but not limited to, the ICH guideline for GCP, consensus ethical principles derived from the Declaration of Helsinki, and applicable laws and regulations.

Patient Disposition

A total of 421 subjects were enrolled into the study, including 212 (50.4%) in the lotilaner ophthalmic solution group and 209 (49.6%) in the vehicle group.

Study TRS-009: Subject Disposition (All Randomized Subjects)

	TP-03	**Vehicle**
Randomized, n	212	209
Cohort 1	143	144
Cohort 2	69	65
Completed, n (%)[a]	208 (98.1)	203 (97.1)
Cohort 1	140 (97.9)	139 (96.5)
Cohort 2	68 (98.6)	64 (98.5)
Reason for discontinuation, n (%)[a]	4 (1.9)	6 (2.9)
Adverse event	1 (0.5)	2 (1.0)
Exclusion criterion	1 (0.5)	0
Reasons relating to COVID-19	2 (0.9)	2 (1.0)
Other	0	2 (1.0)[b]
Cohort 1: Reason for discontinuation, n (%)[c]	3 (1.4)	5 (2.4)
Adverse event	0	2 (1.4)
Exclusion criterion	1 (0.7)	0
Reasons relating to COVID-19	2 (1.4)	2 (1.4)
Other	0	1 (0.7)[d]
Cohort 2: Reason for discontinuation, n (%)e	1 (1.4)	1 (1.5)
Adverse event	1 (1.4)	0
Exclusion criterion	0	0
Reasons relating to COVID-19	0	0
Other	0	1 (1.5)[f]

COVID-19 = coronavirus disease 2019
[a] Percentages were based on the total number of randomized subjects.
[b] Other = consent withdrawal and lost to follow-up.
[c] Percentages were based on the total number of subjects randomized to Cohort 1.
[d] Other = consent withdrawal
[e] Percentages were based on the total number of subjects randomized to Cohort 2.
[f] Other = lost to follow-up
Source: Table 14.1.1, Listing 16.2.1 and table 6 TRS-009 CSR

Protocol Violations/Deviations

The only protocol deviations that occurred in more than 5 subjects each were having a visit occur outside the allowed window (18 subjects total [4.3%]) and improper protocol procedures conducted at the study center (17 subjects total [4.0%]). These deviations occurred in similar numbers of subjects in each study drug group.

Study TRS-009: Summary of Protocol Deviations (All Randomized Subjects)

	TP-03	Vehicle
	N = 212	N = 209
	n (%)	n (%)
Any deviation	33 (15.6)	21 (10.0)
Major	1 (0.5)	0
Minor	33 (15.6)	21 (10.0)
COVID-19 related	8 (3.8)	1 (0.5)

COVID-19 = coronavirus disease 2019
Severities of the deviations, irrespective of their potential to affect the primary efficacy endpoint analysis, were assigned by the sponsor prior to database lock and unmasking. Subjects with multiple deviations were only counted once in each category.
Source: Table 14.1.1 TRS-009 CSR

Study TRS-009: Demographic and Baseline Characteristics (Full Analysis Set)

	TP-03 N = 212	Vehicle N = 209	Total N = 421
Age			
Mean (SD)	66.1 (12.09)	67.8 (12.63)	67.0 (12.37)
Min, max	19, 91	22, 94	19, 94
< 65 years, n (%)	86 (40.6)	65 (31.1)	151 (35.9)
≥ 65 years, n (%)	126 (59.4)	144 (68.9)	270 (64.1)
Sex, n (%)			
Male	89 (42.0)	92 (44.0)	181 (43.0)
Female	123 (58.0)	117 (56.0)	240 (57.0)
Childbearing potential, n (%)[a]			
Yes	8 (6.5)	8 (6.8)	16 (6.7)
No	115 (93.5)	109 (93.2)	224 (93.3)
Ethnicity, n (%)			
Hispanic or Latino	14 (6.6)	11 (5.3)	25 (5.9)
Not Hispanic or Latino	198 (93.4)	198 (94.7)	396 (94.1)
Race, n (%)			
American Indian or Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Asian	3 (1.4)	2 (1.0)	5 (1.2)
Black or African American	11 (5.2)	16 (7.7)	27 (6.4)
White	195 (92.0)	187 (89.5)	382 (90.7)
Multiple Race	2 (0.9)	3 (1.4)	5 (1.2)

max = maximum; min = minimum; SD = standard deviation
[a] Percentages were based on the number of female subjects.
Source: Table 14.1.2.1.1 TRS-009 CSR

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of demodex blepharitis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Study TRS-009: Collarette Score, Erythema Score, and Mite Density for the Analysis Eye at Screening (Full Analysis Set, Observed Data)

	Lotilaner N=212	Vehicle N=209
Collarette scores (upper eyelid), n (%)a		
2	85 (40.1)	74 (35.4)
3	80 (37.7)	97 (46.4)
4	47 (22.2)	38 (18.2)
Erythema score (upper eyelid), n (%)[b]		
1	114 (53.8)	112 (53.6)
2	91 (42.9)	90 (43.1)
3	7 (3.3)	7 (3.3)
Mite density[c]		
Mean (SD)	3.185 (1.6735)	3.164 (1.5947)
Median	2.750	2.750
Min, max	1.50, 10.00	1.50, 10.75

max = maximum; min = minimum; SD = standard deviation
[a] Study eligibility required subjects to have a collarette score for the upper eyelid of the analysis eye ≥ 2 (i.e., > 10 lashes with collarettes present). No subject in the study had a collarette score of 0 or 1 at baseline.
[b] Study eligibility required subject to have at least mild erythema in the upper eyelid of the analysis eye (i.e., an erythema score ≥ 1).
[c] Study eligibility required subjects to have a *Demodex* density in the analysis eye (upper and lower eyelids combined) of ≥ 1.5 mites/lash.
Source: Table 14.2.2.1.2, Table 14.2.7.99.3, and Table 14.2.6.1 TRS-009 CSR

Baseline ocular assessment results were generally similar across all treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study TRS-009: Study Drug Compliance (Safety Analysis Set)

	TP-03 N=212	Vehicle N=209
Compliance (%)		
Mean (SD)	98.97 (3.065)	99.44 (1.682)
Min, max	73.5, 101.2	88.2, 103.0
Categorical Summary, n (%)		
Compliant	210 (99.1)	209 (100.0)
Noncompliant	2 (0.9)	0

Across study drug groups, 24.9% of the subjects used at least 1 ocular concomitant medication and 95.2% of the subjects used at least 1 non-ocular concomitant medication. No important differences were observed between study drug groups based on a review of the 3 most frequently reported ocular and non-ocular concomitant medications.

Efficacy Results – Primary Endpoint

The primary endpoint of Study TRS-009 was the proportion of subjects achieving a cure (collarette score = 0) in the upper eyelid of the analysis eye at Day 43 (Full Analysis Set).

Study TRS-009: Primary Efficacy Endpoint – Proportion of Subjects Achieving a Cure (Collarette Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	Lotilaner N = 212	Vehicle N = 209
Cured (collarette score = 0), N (%) (SE)	93 (44%) (3.4)	15 (7%) (1.8)
Difference in proportion cured (SE)[a]	0.3669 (0.0386)	
p-value[b]	< 0.0001	

SE = standard error
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.
[a] The difference was computed as TP-03 minus vehicle.
[b] The p-value was from a difference of proportions test.
Source: Table 14.2.2.1.1 TRS-009 CSR

TP-03 is statistically superior to vehicle in the elimination of collarettes from the upper eyelid.

A total of 5 sensitivity analyses were used to evaluate the robustness of the primary efficacy analysis. The results of all sensitivity analyses were similar to one another and to the primary analysis in regard to the difference between study drug groups in the percentage of subjects achieving a cure at Day 43.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Study TRS-009 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.

Study TRS-009: 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 Cure (Collarette and Erythema Scores = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	Lotilaner	Vehicle
Eradication of *Demodex* mites	N=209	N=204
Cured (mite density = 0), (%) (SE)	142 (68%) (3.2)	36 (17%) (2.6)
Difference in proportion cured (SE)[a]	0.5046 (0.0416)	
p-value[b]	< 0.0001	
Composite cure	N=209	N=204
Cured (collarette and erythema scores =0), (%) (SE)	29 (14%) (2.4)	2 (1%) (0.7)
Difference in proportion cured (SE)[a]	0.1291 (0.0249)	
p-value[b]	< 0.0001	

SE = standard error
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.
[a] The difference was computed as TP-03 minus vehicle.
[b] The p-value was from a difference of proportions test.
Source: Table 14.2.3.1.1 and Table 14.2.4.1.1 TRS-009 CSR

The statistical analysis plan allowed for evaluation of the two prespecified secondary endpoints using the Hochberg procedure. The secondary endpoint evaluation shows that lotilaner ophthalmic solution also demonstrates statistical significance over vehicle for both eradication of mites and the composite score of collarette elimination with cure of erythema.

Sensitivity analyses were used to evaluate the robustness of the secondary efficacy analyses. In these analyses, missing data was imputed as failures. The results of each sensitivity endpoint analysis were similar to the results for the same endpoint in the primary analysis. The difference between study drug groups in the eradication of Demodex mites at Day 43 was ~49.8%, while the difference between study drug groups in the percentage of subjects achieving a composite cure at Day 43 was ~12.7%; p<0.0001 in the pairwise comparisons of study drug groups for each endpoint.

Dose/Dose Response

Dose response was not evaluated in this development program.

Durability of Response

Proportion of Subjects Cured (Collarette Grade 0)

	Lotilaner	Vehicle
Screening	0/212= 0%	0/209= 0%
Day 8	4/211= 2%	4/208= 2%
Day 15	21/204=10%	3/208= 1.4%
Day 22	38/207=18%	4/206= 2%
Day 43	92/209=44%	15/204= 7%
Day 57	35/68= 51%	4/ 64= 6%

Additional Analyses Conducted on the Individual Trial

A post hoc analysis was conducted to evaluate the proportion of subjects who achieved an erythema score of 0 on Day 43 since erythema is an accepted sign endpoint for blepharitis; and elimination of erythema would be an indication of improvement.

Study TRS-009: Post Hoc Efficacy Analysis – Proportion of Subjects Achieving a Cure (Erythema Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	Lotilaner N = 212	**Vehicle N = 209**
Cured (erythema score = 0), % (SE)	19.2% (2.7)	7.1% (1.8)
Difference in proportion cured (SE)[a]	0.1205 (0.328)	
~~p-value~~[b]	~~0.0002~~	

SE = standard error
Study drug withdrawal 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 an erythema score of 0 at Day 43.
[a] The difference was computed as lotilaner ophthalmic solution minus vehicle.
[b] The p-value was from a difference of proportions test.
Source: Table 14.2.7.99.1 TRS-009 CSR

The P value is not applicable as this was a post hoc analysis.

6.2. TRS-010 (Saturn-2)

6.2.1. Study Design

Studies TRS-009 and TRS-010 shared identical inclusion/exclusion criteria, efficacy assessments and methods (i.e., scoring scales and evaluation procedures), randomized study drugs (lotilaner ophthalmic solution or vehicle), and treatment durations; the efficacy endpoints evaluated in each study were also nearly identical. Refer to section 6.1 for the study design. The comparison of the efficacy endpoints is presented in the table below.

Pivotal Studies: Primary and Secondary Efficacy Endpoints

Study TRS-009 (Saturn-1)	**Study TRS-010 (Saturn-2)**
Primary	
• Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43	• Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43
Secondary	
• Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Day 43 • Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred to as a composite cure)	• Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Day 43 • Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred to as a composite cure) • Proportion of subjects cured based on an erythema score of 0 for the upper eyelid of the analysis eye at Day 43[a]

Protocol Amendments

Revision 1 (Protocol Version 2.0):

- Indicated that blood sample collection for hematology and blood chemistry, and urine sample collection for urinalysis, was conducted only at selected study centers
- Added an inclusion criterion that subjects who participated in the Saturn-1 clinical study could not participate in the Saturn-2 clinical study
- Added an exclusion criterion of ocular surgery within 3 months of screening that, in the opinion of the investigator, could impact subject safety or data validity
- Added clarification that block stratification by study center was being used in the interactive response technology system
- Clarified that the randomization number once assigned could not be reused
- Corrected hospitalization duration to be considered an SAE from 23 to 24 hours
- Added action taken with the investigational product when an AE occurred as: none, drug temporarily withdrawn, drug discontinued, and unknown

- Added text to clarify what collarettes should be included in the collarette count
- Added text to provide examiners discretion in the order of testing for eyelid photos
- Added a list of hematology and blood chemistry tests that could be conducted
- Added text that drug concentration analysis would be conducted at selected study centers
- Updated the list of urinalysis tests that could be conducted

Revision 2 (Protocol Version 3.0):

- Deleted the Day 57 visit for tertiary endpoints
- Defined Cohorts 1 and 2 as: Cohort 1 was all subjects who completed the Day 57 visit prior to protocol version 3. Cohort 2 was all subjects after protocol version 3 who were not required to complete a Day 57 visit.
- Increased the potential number of study centers by 5 to help with speed of enrollment.
- Clarified that the Day 57 visit should only be conducted for Cohort 1 and that the Day 90 visit should only be conducted at study centers that performed specular microscopy
- Clarified that endothelial cell density was only conducted at selected study centers
- Clarified that Day 43 was the end of study for Cohort 2 subjects at study centers not performing specular microscopy
- Clarified that Day 57 assessments were performed for Cohort 1 subjects only, and that this visit was the end of study for Cohort 1 subjects at study centers not performing specular microscopy
- Clarified that Day 90 was the end of study for subjects at study centers performing specular microscopy
- Clarified that if screening and Day 1 activities were performed on the same day, that concomitant medication review did not have to be repeated
- Changed lock date for study data from Day 57 to Day 43 Revision 3 (Protocol Version 4.0):
- Added erythema cure for the upper eyelid of the analysis eye at Day 43 as a secondary endpoint based on an erythema score of zero
- Clarified that Demodex mite eradication is based on mite density of 0 mites/lash from the analysis eye
- Added corneal staining as a safety assessment
- Added a more recent Phase 2b/3 study (TRS-009 [Saturn-1]) as a justification for sample size
- Clarified the interpretation of the Hochberg testing method for the secondary endpoints

Study TRS-010: Schedule of Assessments

Procedures	Screening Day −14 to 1	Enrollment / Day 1	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 −3/+4 days	Day 43 −3/+7 days	Day 57 −6/+14 days	Day 90 ± 14 days[a]
Informed consent	X							
Demographics	X							
Medical/ophthalmic history	X							
Concomitant medication review	X	X[b]	X	X	X	X	X	X
Drop comfort		X	X	X	X	X		
Corrected distance visual acuity	X	X[b]	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X[b]	X	X	X	X	X	X
Collarette and eyelid margin erythema grading	X		X	X	X	X	X	
Corneal fluorescein staining		X	X	X	X	X	X	
Intraocular pressure		X				X	X	
Demodex count	X			X	X	X	X	
Specular microscopy (at selected study centers)		X				X		X
Eyelid photos (at selected study centers)		X				X	X	
Hematology and blood chemistry analyses (at selected study centers)		X				X		
Drug concentration analysis (at selected study centers)						X		
Urinalysis (at selected study centers)		X				X		
Urine pregnancy test[c]	X					X		
Randomization		X						
Dispense study drug; diary		X						
Collection and review of subject diary			X	X	X			
Adverse event review and evaluation		X	X	X	X	X	X	X
Collect study drug; diary						X		
Study exit						X[d]	X[e]	X[f]

[a] At study centers performing specular microscopy
[b] If the screening and Day 1 visits were completed on the same day, this procedure did not have to be repeated.
[c] Female subjects of childbearing potential only.
[d] Study exit for subjects in Cohort 2 if study center was not performing specular microscopy.
[e] Study exit for subjects in Cohort 1 if study center was not performing specular microscopy.
[f] Study exit for subjects at study centers performing specular microscopy.

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with the protocol and recognized standards including, but not limited to, the ICH guideline for GCP, consensus ethical principles derived from the Declaration of Helsinki, and applicable laws and regulations.

Patient Disposition

	TP-03	Vehicle	Total

Randomized, n	203	209	412
Randomized and dosed	203	209	412
Randomized and not dosed	0	0	0
Completed, n (%)[a]	36 (17.7)	37 (17.7)	73 (17.7)
Discontinued, n (%)[a]	10 (4.9)	9 (4.3)	19 (4.6)
Ongoing	157 (77.3)	163 (78.0)	320 (77.7)
Reason for discontinuation, n (%)[a]			
Adverse event	2 (1.0)	1 (0.5)	3 (0.7)
Other[b]	8 (3.9)	8 (3.8)	16 (3.9)

[a] Percentages were based on the total number of randomized subjects.
[b] Specific reasons for "other" are provided within Listing 16.2.1.
Source: Table 14.1.1 and Listing 16.2.1

The number of subjects that discontinued the study was similar between the treatment groups.

Protocol Violations/Deviations

The only protocol deviations that occurred in more than 5 subjects each were improper protocol procedures at the study center (199 subjects total [48.3%]), having a visit occur outside the allowed window (43 subjects total [10.4%]), issues with informed consent (14 subjects total [3.4%]), inclusion/exclusion and randomization (9 subjects total [2.2%]). The deviations occurred in similar numbers of subjects in each study drug group.

Study TRS-010: Summary of Protocol Deviations (All Randomized Subjects)

	Lotilaner N = 203 n (%)	**Vehicle N = 209 n (%)**
Any deviation	113 (55.7)	123 (58.9)
Major	7 (3.4)	5 (2.4)
Minor	111 (54.7)	121 (57.9)
COVID-19 related	2 (1.0)	3 (1.4)

Severities of the deviations, irrespective of their potential to affect the primary efficacy endpoint analysis, were assigned by the sponsor prior to database lock and unmasking. Subjects with multiple deviations were only counted once in each category.
Source: CSR Table 14.1.1

Table of Demographic Characteristics (Full Analysis Set)

	Lotilaner N = 203	Vehicle N = 209
Age		
Mean (SD)	63.9 (15.15)	65.1 (13.35)
Min, max	18, 88	24, 89
< 65 years, n (%)	84 (41.4)	80 (38.3)
≥ 65 years, n (%)	119 (58.6)	129 (61.7)
Sex, n (%)		
Male	106 (52.2)	106 (50.7)
Female	97 (47.8)	103 (49.3)
Childbearing Potential, n (%)[a]		
Yes	10 (10.3)	8 (7.8)
No	87 (89.7)	95 (92.2)
Ethnicity, n (%)		
Hispanic or Latino	17 (8.4)	17 (8.1)
Not Hispanic or Latino	186 (91.6)	192 (91.9)
Race, n (%)		
American Indian or Alaska Native	1 (0.5)	1 (0.5)
Asian	3 (1.5)	3 (1.4)
Black or African American	20 (9.9)	15 (7.2)
Native Hawaiian or Other Pacific Islander	2 (1.0)	0
White	176 (86.7)	187 (89.5)
Other	0	3 (1.4)
Multiple Race	1 (0.5)	0

max = maximum; min = minimum; SD = standard deviation
[a] Percentages were based on the total number of female subjects.
Source: Table 14.1.2.1.1 TRS-010 CSR.

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of demodex blepharitis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Study TRS-010: Collarette Score, Erythema Score, and Mite Density for the Analysis Eye at Screening (Full Analysis Set, Observed Data)

	TP-03 N=203	Vehicle N=209
Collarette scores (upper eyelid), n (%)[a]		
2	72 (36)	64 (31)
3	80 (39)	77 (37)
4	51 (25)	68 (33)
Erythema score (upper eyelid), n (%)[b]		
1	107 (53)	99 (47)
2	80 (39)	94 (45)
3	16 (8)	16 (8)
Mite density[c]		
Mean (SD)	3.2 (1)	3 (1.7)
Median	2.8	3
Min, max	1.5, 8.8	0.5, 10

[a] Study eligibility required subjects to have a collarette score for the upper eyelid of the analysis eye ≥ 2 (ie, > 10 lashes with collarettes present). No subject in the study had a collarette score of 0 or 1 at baseline.
[b] Study eligibility required subject to have at least mild erythema in the upper eyelid of the analysis eye (ie, an erythema score ≥ 1).
[c] Study eligibility required subjects to have a *Demodex* density in the analysis eye (upper and lower eyelids combined) of ≥ 1.5 mites/lash.
Source: Table 14.2.2.7, Table 14.2.3.3.3, and Table 14.2.4.2 TRS-010 CSR

Study TRS-010: Study Drug Compliance (Safety Analysis Set)

	TP-03 N=203	Vehicle N=209
Compliance (%)		
Mean (SD)	98.65 (5.259)	98.49 (5.615)
Min, max	33.7, 101.2	33.0, 102.4
Categorical Summary, n (%)		
Compliant	202 (99.5)	207 (99.0)
Noncompliant	1 (0.5)	2 (1.0)

max = maximum; min = minimum; SD = standard deviation
In this study, compliant was defined as using ≥ 80% to ≤ 125% of the expected number of study drug instillations, noncompliant was defined as using < 80% of the expected number of study drug instillations, and over compliant was defined as using > 125% expected number of study drug instillations.
Source: CSR Table 14.2.1.1

Across study drug groups, 32% of the subjects used at least 1 ocular concomitant medication and 90% of the subjects used at least 1 non-ocular concomitant medication. No important differences were observed between study drug groups based on a review of the most frequently reported ocular and non-ocular concomitant medications.

Baseline ocular assessment results and drug compliance were generally similar across all treatment groups.

Efficacy Results – Primary Endpoint

Study TRS-010: Primary Efficacy Endpoint – Proportion of Subjects Achieving a Cure (Collarette Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	TP-03 N = 203	Vehicle N = 209
Cured (collarette score = 0), % (SE)	111 (55%) (3.5)	25 (12%) (2.3)
Difference in proportion cured (SE)[a]	0.4250 (0.0422)	
p-value[b]	< 0.0001	

SE = standard error
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.
[a] The difference was computed as lotilaner ophthalmic solution minus vehicle.
[b] The p-value was from a difference of proportions test.
Source: CSR Table 14.2.2.1

Lotilaner ophthalmic solution is statistically superior to vehicle in the elimination of collarettes from the upper eyelid.

A total of 5 sensitivity analyses were used to evaluate the robustness of the primary efficacy analysis. The results of all sensitivity analyses were similar to one another and to the primary analysis in regard to the difference between study drug groups in the percentage of subjects achieving a cure at Day 43 (Table 13). Specifically, the magnitude of the differences between study drug groups across sensitivity analyses ranged from ~41.2% to ~43.5%; $p < 0.0001$ in all pairwise comparisons.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Study TRS-010 had three pre-specified secondary endpoints. The endpoints were the proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Day 43. The proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred to as a composite cure), and the proportion of subjects cured based on an erythema score of 0 for the upper eyelid of the analysis eye at Day 43.

Study TRS-010: Secondary Efficacy Endpoints – Proportion of Subjects with Eradication of *Demodex* Mites, Proportion of Subjects Achieving a Composite Cure (Collarette and Erythema Scores = 0), and Proportion of Subjects Achieving a Cure (Erythema Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (Full Analysis Set)

	Lotilaner N=203	Vehicle N=209
Eradication of *Demodex* mites (mite density = 0), % (SE)	50% (3.6)	14% (2.4)
Difference in proportion cured (SE)[a]	0.3588 (0.0432)	
p-value[b]	< 0.0001	
Composite Cure (collarette and erythema scores = 0), % (SE)	19% (2.8)	4% (1.4)
Difference in proportion cured (SE)[a]	0.1482 (0.0309)	
p-value[b]	< 0.0001	
Erythema Cure (erythema score = 0), % (SE)	30% (3.3)	9% (2.0)
Difference in proportion cured (SE)[a]	0.2116 (0.0384)	
p-value[b]	< 0.0001	

SE = standard error
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.
[a] The difference was computed as lotilaner ophthalmic solution minus vehicle.
[b] The p-value was from a difference of proportions test.
Source: Table 14.2.3.1.1, Table 14.2.3.2.1, and Table 14.2.3.3.1

The statistical analysis plan 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 .

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

Dose/Dose Response

Dose response was not evaluated in this development program.

Durability of Response

Durability of Response

Proportion of Subjects Cured (Collarette Grade 0)

	Lotilaner	Vehicle
Screening	0/203= 0%	0/209= 0%
Day 8	7/196= 4%	7/206= 3%
Day 15	35/192=18%	7/201= 3.5%
Day 22	55/195=18%	12/200= 6%
Day 43	108/209=56%	25/200= 12.5%
Day 57	64/122=52%	10/ 125= 8%

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Two trials (TRS-009 and TRS-010) were submitted with this NDA to support the approval of lotilaner for the treatment of demodex blepharitis. Endpoints for this indication should ensure that the symptoms associated with demodex blepharitis have been completely resolved. The endpoints that can show a clinically relevant benefit include complete resolution of eyelash collarettes, eradication of eyelash mites, and resolution of eyelid erythema.

TRS 009 (Saturn-1) demonstrated efficacy of lotilaner ophthalmic solution by showing complete resolution of eyelash collarettes for the primary endpoint in addition to the secondary endpoints of mite eradication and composite score (collarettes and eyelid erythema). TRS-010 (Saturn-2), demonstrated efficacy by showing complete resolution of eyelash collarettes for the primary endpoint in addition to the secondary endpoints of mite eradication, erythema and composite score (collarettes and eyelid erythema).

The results of these clinical trials support the use of TP-03 (lotilaner ophthalmic solution), 0.25% for the treatment of demodex blepharitis.

8. Review of Safety

8.1. Safety Review Approach

The primary source for safety data for lotilaner ophthalmic solution was from the two multidose studies used for the efficacy analysis: TRS-090 (Saturn-1) and TRS-010 (Saturn-2) See section 5.1. In addition, the sponsor conducted a PK study TRS-012 (Hyperion); the safety results of the PK study were consistent with the phase 3 trials and are not integrated into the pooled data. The results of earlier pilot studies conducted were not representative of the dose or duration as proposed for marketing.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In the pivotal 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 (96.8%) 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 pivotal studies.

Studies TRS-009 and TRS-010: Subject Disposition (All Randomized Subjects)

	TRS-009		**TRS-010**	
	TP-03	**Vehicle**	**TP-03**	**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 TRS-009 and subjects in Cohort 1 of Study TRS-010 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 TRS-009 Cohort 2 and Study TRS-010 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 TRS-009 Cohort 2 or TRS-010 Cohort 1 were counted as not having completed the Day 57 visit.
Source: ISS, Table 1.1; TRS-009 CSR, Section 7.1; TRS-010 CSR, Section 7.1

Studies TRS-009 and TRS-010: Extent of Exposure (Safety Analysis Set)

Exposure (days)	TP-03 N = 415	Vehicle N = 418
Mean (SD)	42.7 (6.85)	42.8 (5.85)
Median	43.0	43.0
Min, max	1, 50	1, 55

max = maximum; min = minimum; SD = standard deviation
The extent of exposure was calculated in days as the date of the last dose (or last recorded dose for subjects who were lost to follow-up) minus the date of the first dose, plus 1.
Source: ISS, Table 2.1

A total of 415 subjects were exposed to lotilaner ophthalmic solution twice a day for 6 weeks which is the proposed treatment dosage and duration. Both studies were conducted with the to-be-marketed formulation.

8.2.2. Relevant characteristics of the safety population:

See Demographic and Baseline Characteristics in sections 6.1.2 and 6.2.2

8.2.3. Adequacy of the safety database:

The overall exposure to lotilaner ophthalmic solution dosed twice per day for at least 4 weeks was 726 subjects throughout the development program. The size of this database and the clinical evaluations conducted during development were adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This NDA submission was of sufficient quality to perform a substantive review of this product.

8.3.2. Categorization of Adverse Events

Adverse events for all studies were coded according to the MedDRA dictionary. A treatment emergent adverse event (TEAE) was defined as any AE that was new or worsened in severity after the first dose of study drug. Treatment-emergent AEs were categorized by system organ class (SOC) and preferred term (PT), seriousness, severity, and relationship to study drug.

8.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns associated with the treatment of ophthalmic conditions (i.e., biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product.

8.4. Safety Results

8.4.1. 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.

8.4.2. Serious Adverse Events

Studies TRS-009 and TRS-010: Treatment-Emergent Serious Adverse Events (Safety Analysis Set)

Preferred term	**TP-03 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.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Thirteen (13) subjects (1.8%) in the overall OC-01 group and 3 subjects (0.9%) in the placebo group discontinued the study due to an adverse event. The number of subjects that discontinued in each of the OC-01 treatment groups were similar.

Of the subjects with SAEs, 6 completed the study, 1 discontinued due to a protocol violation, and the remaining 3 discontinued due to the SAEs (pneumonia [which occurred after completion of study drug administration and the Day 43 visit], vascular access site pseudoaneurysm and

diabetic retinopathy).

Studies TRS-009 and TRS-010: Treatment-Emergent Adverse Events Leading to Study Dropout (Safety Analysis Set)

Treatment Group Subject ID/gender/age (years)/ race	TEAE preferred term	Study Day	Study
Lotilaner ophthalmic solution			
(b) (6) F/73/W	pneumonia	64	TRS-090
M/70/W	visual acuity decreased, iris neovascularization	25	TRS-010
F/50/W	asthma	8	TRS-010
Vehicle			
(b) (6) M/78/W	pseudoaneurysm	75	TRS-090
F/62/W	dry eye	29	TRS-090
M/54/W	headache	16	TRS-010

Table compiled by reviewer using multiple tables in the ISS appendix.

The number of subjects that discontinued across the treatment group were similar. None of the adverse events appear to be related to the treatment drug based on the review of the case report forms.

Studies TRS-009 and TRS-010: Treatment-Emergent Adverse Events Leading to Permanent Study Drug Discontinuation (Safety Analysis Set)

Preferred term	Lotilaner N = 415 n (%)	Vehicle N = 418 n (%)
Dry eye	0	1 (0.2%)
Eyelid pruritus	1 (0.2%)	0
Iris neovascularization	1 (0.2%)	0
Visual acuity reduced	1 (0.2%)	0
Instillation site irritation	1 (0.2%)	0
Pneumonia	1 (0.2%)	0
Vascular access site pseudoaneurysm	0	1 (0.2%)
Headache	0	1 (0.2%)
Asthma	1 (0.2%)	0

Source: ISS, Table 4.2.6.1 and summary of clinical safety Table 11

Twice as many subjects discontinued study drug in the lotilaner ophthalmic solution group compared to vehicle; however, the low numbers and types of events do not raise any issue about the safety of the product.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Studies TRS-009 and TRS-010: Treatment-Emergent Ocular Events Occurring in ≥ 1% of Subjects in Either Study Drug Group by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class Preferred term	Lotilaner N =415 n (%)	Vehicle N = 418 n (%)
Eye disorders	51 (12%)	44 (10%)
Chalazion	4 (1%)	3 (1%)
Eye pain	4 (1%)	3 (1%)
Punctate keratitis	4 (1%)	1 (0.2%)
Dry eye	4 (1%)	3 (1%)
Visual acuity reduced	11 (3%)	11 (3%)
General disorders and administration site conditions	46 (11%)	39 (9%)
Instillation site pain	41 (10%)	30 (7%)
Instillation site pruritus	4 (1%)	8 (2%)
Infections and infestations	4 (1%)	1 (0.2%)
Hordeolum	4 (1%)	1 (0.2%)

PT = preferred term; SOC = system organ class
The table includes only 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%) and reduced visual acuity (3%).

8.4.5. Laboratory Findings

Safety laboratory analyses were conducted only in Study TRS-010. No clinically meaningful trends were observed over time in hematology, chemistry or urinalysis. Variations were noted in some parameters; however, the changes over time were not suggestive of a safety signal.

8.4.6. Vital Signs

Vital sign measurements and physical examinations were performed only in the PK study (TRS-012). In this study, there were no clinically significant or study drug related changes from baseline in vital signs or physical examination findings.

8.4.7. Best Corrected Visual Acuity

Studies TRS-009 and TRS-010: Corrected Distance Visual Acuity Assessments by Study Drug Group and Eye (Safety Analysis Set)

	Lotilaner N = 415		Vehicle N = 418	
	Right Eye	Left Eye	Right Eye	Left Eye
Baseline				
N	413	413	417	417
Mean (SD)	0.118 (0.1615)	0.117 (0.1625)	0.115 (0.1643)	0.108 (0.1567)

Median	0.100	0.100	0.100	0.100
Min, max	-0.30, 0.70	-0.30, 0.62	-0.20, 1.00	-0.24, 0.74
Change from baseline at Day 8				
N	407	407	414	414
Mean (SD)	-0.011 (0.0841)	-0.010 (0.0796)	-0.008 (0.0811)	-0.009 (0.0916)
Median	0.000	0.000	0.000	0.000
Min, max	-0.32, 0.30	-0.28, 0.22	-0.46, 0.30	-0.40, 0.36
Change from baseline at Day 15				
N	396	396	409	409
Mean (SD)	-0.011 (0.0904)	-0.015 (0.0858)	-0.005 (0.0834)	-0.010 (0.0892)
Median	0.000	0.000	0.000	0.000
Min, max	-0.32, 0.26	-0.30, 0.26	-0.40, 0.22	-0.60, 0.30
Change from baseline at Day 22				
N	402	402	406	406
Mean (SD)	-0.018 (0.0872)	-0.027 (0.0949)	-0.016 (0.0886)	-0.020 (0.0883)
Median	-0.020	-0.020	0.000	0.000
Min, max	-0.32, 0.32	-0.42, 0.50	-0.50, 0.20	-0.42, 0.30
Change from baseline at Day 43				
N	401	401	404	404
Mean (SD)	-0.017 (0.0960)	-0.024 (0.0927)	-0.015 (0.0941)	-0.014 (0.0913)
Median	-0.020	-0.020	0.000	0.000
Min, max	-0.52, 0.30	-0.54, 0.28	-0.52, 0.30	-0.46, 0.32
Change from baseline at Day 57				
N	190	190	188	188
Mean (SD)	-0.022 (0.0931)	-0.029 (0.1012)	-0.014 (0.0962)	-0.003 (0.0824)
Median	0.000	-0.020	0.000	0.000
Min, max	-0.30, 0.22	-0.34, 0.28	-0.40, 0.18	-0.24, 0.24

max = maximum; min = minimum; SD = standard deviation
Corrected distance visual acuity was reported using the logarithm of the minimum angle of resolution (logMAR) scale, as assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.
Source: ISS, Table 5.1 and Summary of Clinical Safety Table 12

No clinically relevant changes in visual acuity occurred in either treatment group during the clinical trial.

8.4.8. Intraocular Pressure

Studies TRS-009 and TRS-010: Assessments of Intraocular Pressure by Study Drug Group and Eye (Safety Analysis Set)

	TP-03 N = 415		Vehicle N = 418	
	Right Eye	**Left Eye**	**Right Eye**	**Left Eye**
Baseline				
N	415	415	418	418
Mean (SD)	15.2 (3.12)	15.2 (2.88)	15.1 (3.03)	15.1 (2.87)
Median	15.0	15.0	15.0	15.0
Min, max	7, 24	6, 23	6, 25	7, 25
Change from baseline at Day 43				
N	402	402	404	404
Mean (SD)	0.0 (3.11)	-0.2 (2.90)	0.0 (2.83)	-0.1 (2.77)

Median	0.0	0.0	0.0	0.0
Min, max	-11, 13	-12, 13	-8, 11	-8, 13
Change from baseline at Day 57				
N	190	190	189	189
Mean (SD)	-0.4 (3.06)	-0.3 (2.85)	-0.5 (3.13)	-0.5 (3.00)
Median	0.0	0.0	-1.0	0.0
Min, max	-8, 8	-8, 8	-8, 10	-9, 10

Summary of Clinical Safety Table 13
max = maximum; min = minimum; SD = standard deviation
Intraocular pressure measurements were reported in mmHg. Baseline was defined as the last nonmissing measurement available prior to the initiation of randomized study drug.
Source: ISS, Table 6

No clinically relevant changes in intraocular pressure occurred in either treatment group during the clinical trial.

8.4.9. 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. There were no clinically relevant changes in endothelial cell density (ECD) observed in either treatment group up to day 43. Study TRS-010 is ongoing and includes a safety follow-up visit at Day 90. Additional ECD data will be included in the 120-day safety update.

8.4.10. Electrocardiograms (ECGs)

Electrocardiograms were performed only in the PK study. In this study, there were no clinically significant or study drug related changes from baseline in ECG parameters.

8.4.11. QT

QT/IRT review pending

8.5. Analysis of Submission-Specific Safety Issues

There are no submission specific safety issues requiring additional analysis.

8.6. Safety Analyses by Demographic Subgroups

To evaluate the effect of intrinsic factors on the safety profile of lotilaner ophthalmic solution, study drug exposure and TEAEs (ocular and non-ocular) in the pooled phase 3 studies were summarized by age (< 65 years vs ≥ 65 years), sex, race (White vs non-White), ethnicity (Hispanic or Latino vs not Hispanic or Latino), and iris color (blue vs not blue).

There were no clinically meaningful safety issues raised in any of the subgroup analyses.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies have been conducted with lotilaner for this NDA. A waiver for carcinogenicity studies is being requested as part of this submission. See non-clinical review for determination.

8.7.2. Human Reproduction and Pregnancy

No adequate and well-controlled trials of lotilaner have been conducted in pregnant or lactating women; however, systemic exposure to lotilaner from ocular administration following 6 weeks of topical ocular administration is low is > 99% plasma protein bound.

8.7.3. Pediatrics and Assessment of Effects on Growth

Demodex blepharitis is rare in the pediatric population. The applicant has 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.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Lotilaner ophthalmic solution ophthalmic solution is not approved or marketed in any country.

8.8.2. Expectations on Safety in the Postmarket Setting

There are no expected potential safety issues of concern. There are no recommended Post-marketing Requirements or Phase 4 Commitments.

8.8.3. Additional Safety Issues From Other Disciplines

N/A – all safety issues have adequately been addressed in this review.

8.9. Integrated Assessment of Safety

The overall exposure to lotilaner ophthalmic solution dosed twice per day for at least 4 weeks was 726 subjects throughout the development program. In the phase 3 trails, 415 subjects were treated with the to-be-marketed lotilaner ophthalmic solution 0.25%. 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%). 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.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for the NDA.

10. Risk Evaluation and Mitigation Strategies (REMS)

There are no Risk Evaluation or Mitigation strategies recommended for this NDA.

11. Post-marketing Requirements and Commitments

There are no Post-marketing Requirements or Commitments recommended for this NDA.

12. Appendices

12.1. Financial Disclosure

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 S 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)

12.2. List of Clinical Investigators

TRS-009 (Saturn-1)

Study Center	Principal Investigator	Study Center Address	Number of Subjects
02	David L Wirta, MD	Eye Research Foundation 520 Superior Ave, Suite 235 Newport Beach, CA 92663	43
03	Gail L Torkildsen, MD	Andover Eye Associates 138 Haverhill Street, Suite 104 Andover, MA 01810	6
04	Blair Boehmer, MD	Midwest Cornea Associates, LLC 10300 N Illinois Street, Suite 1020 Carmel, IN 46290	23
05	John C Meyer, MD	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	61
06	James Paauw, MD	Piedmont Eye Center 116 Nationwide Drive Lynchburg, VA 24502	71
07	Jung Dao, MD	Cornea and Cataract Consultants of Arizona 3815 E Bell Road, Suite 2500 Phoenix, AZ 85032	9
08	Patrick Vollmer, OD, FAAO	Vita Eye Clinic 222 N Lafayette St, Suite 12 Shelby, NC 28150	28
09	Carol Aune, OD	Oculus Research Inc at Eyecare Center 4170 Fayetteville Rd Raleigh, NC 27603	20
10	Blake Simmons, OD, FAAO	Vision Institute 320 E Fontanero St, Suite 201 Colorado Springs, CO 80907	34
11	David G Evans, OD	Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	8
12	Daniel V Zimmer, MD, FACS	Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066	50
15	Ehsan Sadri, MD	Visionary Eye Institute 361 Hospital Rd, #324 Newport Beach, CA 92663	7
16	Gregg J Berdy, MD, FACS	Ophthalmology Associates 12990 Manchester Rd, Suite 200 St. Louis, MO 63131	26

17	William E Whitson, MD	Michael Washburn Center for Ophthalmic Research, LLC 901 E. 86th St. Indianapolis, IN 46240	18
18	Jared Peterson, MD	Alpine Research Organization, Inc 124 South Fairfield Road, Suite C Layton UT 84041	17

TRS-010 (Saturn-2)

Study Center	Principal Investigator	Study Center Address	Number of Subjects
05	John C Meyer, MD	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	19
08	Patrick Vollmer, OD, FAAO	Vita Eye Clinic 222 N Lafayette St, Suite 12 Shelby, NC 28150	79
10	Blake Simmons, OD, FAAO	Vision Institute 320 E Fontanero St, Suite 201 Colorado Springs, CO 80907	24
16	Gregg J Berdy, MD, FACS	Ophthalmology Associates 12990 Manchester Rd, Suite 200 St. Louis, MO 63131	32
17	William E Whitson, MD	Michael Washburn Center for Ophthalmic Research, LLC 901 E 86th Street Indianapolis, IN 46240	10
18	Jared Peterson, MD	Alpine Research Organization 1407 N 2000 W, Suite A Clinton, UT 84015	34
19	Blair Boehmer, MD	Pankratz Eye Institute 3135 Middle Drive Columbus, IN 47203	5
22	Scott Schecter, OD	Pinnacle Research Institute 2900 West Cypress Creek Road, Suite 10 Fort Lauderdale, FL 33309	63
23	Cassandra Ortiz, OD	New River Vision Care 1001 Elizabeth Street Oak Hill, WV 25901	15
24	Aimee Edell, MD	East Bay Eye Center 5801 Norris Canyon Drive, Suite 200 San Ramon, CA 94583	9
25	Gina Wesley, OD	Complete Eye Care of Medina 170 Westfalen Trail Medina, MN 55340	3

26	Jackson Lever, MD	Alpine Research Organization, Inc./Country Hills Eye Center 875 Country Hills Drive Ogden, UT 84403	10
27	Joseph Tauber, MD	Tauber Eye Center 4400 Broadway Boulevard Kansas City, MO 64111	5
28	Shane Kannarr, OD	Kannarr Eye Center 2521 North Broadway Street Pittsburg, KS 66762	13
29	Aynsley Girardeau, OD	Pure Ophthalmic Research 7014 Tutor Street, Suite C Mint Hill, NC 28227	10
30	Mitchell Jackson, MD	Jackson Eye, S.C. 300 North Milwaukee Avenue, Suite L Lake Villa, IL 60046	6
32	Michael A Samuels, OD	NC Eye Associates 1429 Kelly Road Apex, NC 27502	29
33	Laura Periman, MD	Periman Eye Institute 320 West Galer Street, Suite 201 Seattle, WA 98119	17
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35	Robin Ross, MD	Global Retina Institute 4835 East Cactus Road, Suite 105 Scottsdale, AZ 85254	8
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/s/

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05/03/2023 09:42:18 AM