CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial #:	217603
Drug Name:	XDEMVY™ (Lotilaner Ophthalmic Solution, 0.25%)
Indication(s):	Treatment of Demodex blepharitis
Applicant:	Tarsus, Inc.
Date(s):	Date Submitted: August 25, 2022
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Review Priority:	Standard
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Keywords: Clinical Studies, Efficacy, *Demodex* Blepharitis, difference of proportions test, Pearson's chi-squared test, Paired t-test

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EXECUTIVE SUMMARY

In this original New Drug Application (NDA) submission, the Applicant, Tarsus Pharmaceuticals, Inc. (sponsor) seeks approval of XDEMVY™ (TP-03, Lotilaner Ophthalmic Solution, 0.25%) administered twice daily up 43 days for the treatment of Demodex blepharitis. Data from two pivotal studies, Study TRS-009 (SATURN-1) and Study TRS-010 (SATURN-2), with identically designed multicenter, randomized, double-masked, safety, efficacy, and systemic lotilaner concentration were submitted. In the Study TRS-009 (SATURN-1), there were 212/208 randomized/completed subjects in the TP-03 arm and 209/203 in the vehicle arm; and in the Study TRS-010 (SATURN-2), 203/193 in the TP-03 arm and 209/200 in the vehicle arm.

For both studies, the primary endpoint was the proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43; the secondary 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 collaret and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred a 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 which was proposed only in the Study TRS-010 (SATURN-2). The efficacy endpoints were analyzed using a full analysis set (FAS), which was defined to include all randomized subjects.

Based on the collective efficacy evidence from the two pivotal studies, the reviewer confirmed that a significantly greater percentage of subjects in the TP-03 group achieved a cure (i.e., collarette score = 0) as well as a composite cure (i.e., collarette and erythema scores of 0), an erythema cure (i.e., erythema score = 0) in the upper eyelid of the analysis eye, and an eradication of *Demodex* mites (i.e., mite density = 0) in the analysis eye at Day 43 relative to those in the vehicle group. The results on the primary and secondary endpoints are summarized in the table below.

Overall, this reviewer concluded that the data of the two pivotal studies provided substantial evidence for TP-03 efficacy benefit, applied twice daily (morning and evening) in each eye for 43 days, in the treatment of *Demodex* blepharitis.

Summary of Efficacy Results at Day 43 for Studies TRS-009 and TRS-010: Primary and Secondary Efficacy Endpoints (Full Analysis Set)*

Primary Efficacy Endpoint	**TRS-009**		**TRS-010**	
	TP-03 N=212	**Vehicle N=209**	**TP-03 N=203**	**Vehicle N=209**
Cured (collarett score=0), n (%)	92 (42.9%)	15 (7.2%)	108 (53.2%)	25 (12.0%)
Difference in cured, % (SE)[a]	36.2 (4.2)		41.2 (4.2)	
p-value[b]	<.0001		<.0001	

Secondary Efficacy Endpoints	**TRS-009**		**TRS-010**	
	TP-03 N=212	**Vehicle N=209**	**TP-03 N=203**	**Vehicle N=209**
Eradication of Demodex mites				
Cured (mite density=0), n (%)	142 (67.0%)	36 (17.2%)	100 (49.3%)	29 (13.9%)
Difference in cured, % (SE)[a]	49.8 (3.2)		35.4 (4.6)	
p-value[b]	<.0001		<.0001	
Composite Cure				
Cured (collarette and erythema score=0), n (%)	29 (13.7%)	2 (1.0%)	37 (18.2%)	8 (3.8%)
Difference in cured, % (SE)[a]	12.7 (2.5)		14.4 (3.0)	
p-value[b]	<.0001		<.0001	
Erythema cure[c]				
Cured (erythema score=0), n (%)	40 (18.9%)	14 (6.7%)	60 (29.6%)	18 (8.6%)
Difference in cured, % (SE)[a]	12.2 (3.2)		20.9 (3.7)	
p-value[b]	0.0002		<.0001	

SE = standard error

All endpoints were based on data collected for the analysis eye. The endpoints that evaluated collarette and erythema scores were based on data collected from the upper eyelid.

* Missing Values Viewed as Treatment Failure

b The p-value was from a difference of proportions test

c In Study TRS-009, this analysis was post hoc.

1. INTRODUCTION

OVERVIEW

In this NDA submission, the Applicant, Tarsus Pharmaceuticals, Inc. (Tarsus) seeks approval of XDEMVY™ (Lotilaner Ophthalmic Solution, 0.25%) administered up 43 (57) days for the treatment of Demodex blepharitis.

Blepharitis is a disease characterized by inflammation of the eyelid margins. People with blepharitis often experience lid margin itching, burning, or stinging in the eyes, foreign body sensation, as well as redness of the eyes and eyelids. Blepharitis is commonly associated with infestation of eyelash follicles and meibomian glands by 2 species of microscopic obligate parasitic mites: *Demodex folliculorum* or *Demodex brevis*, respectively. According to published literatures, *Demodex* are the only mites that are known to affect the human eye; the rate of *Demodex* infestation in patients with blepharitis is 44.5% and increases with age.

Currently, there are no FDA approved therapeutics to treat *Demodex* blepharitis. The sponsor developed TP-03 (Lotilaner Ophthalmic Solution), 0.25% for the treatment of *Demodex* Blepharitis. Data of a Phase 2b/3 study and one Phase 3 pivotal study as the overall clinical development were submitted by the sponsor for evaluating the safety and efficacy of TP-03.

Specific Studies Reviewed

A summary of key information for the two pivotal studies which are reviewed in this work is presented as bellow:

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

Source: Sponsor's Clinical Overview Table 1.

Data Sources

Application:	NDA217603
Company	Tarsus Pharmaceuticals, Inc.
Drug	XDEMVY™ (TP-03, Lotilaner Ophthalmic Solution, 0.25%)
CDER EDR link	\\CDSESUB1\evsprod\NDA217603\0001\m5\datasets\
Letter date	8/25/2022

All efficacy data intended to support the approval of TP-03 in the treatment of *Demodex* blepharitis were derived from two pivotal efficacy and safety studies, TRS-009 and TRS-010.

2. STATISTICAL EVALUATION

2.1. DATA AND ANALYSIS QUALITY

The reviewer found the quality and integrity of the submitted data and analysis acceptable.

2.2. EVALUATION OF EFFICACY

In this section, the efficacy assessment for the Study TRS-009 (SATURN-1) and for the Study TRS-010 (SATURN-2) are reviewed for the TP-03 indications, including descriptions of the study designs and the efficacy endpoints, the statistical methodologies used, the summary of patient disposition and demographic and baseline characteristics, and the efficacy analysis. The efficacy variables consisted of collarette grading, eyelid margin erythema grading, and counts of *Demodex* mites.

2.3. STUDY TRS-009 (SATURN-1)

The descriptions about the study design and statistical methodology were from the sponsor.

2.3.1. Study Design and Endpoints

Study Design

The study was a multi-center, randomized, vehicle-controlled, double-blind, parallel-group, Phase 2b/3 study, conducted at 15 study centers in the United States, to evaluate the safety and efficacy of TP-03 for the treatment of Demodex blepharitis.

The analysis eye was defined as the eye that met all inclusion criteria. In the case where both eyes met all criteria, the analysis eye was the eye with the highest Demodex mite density at screening or, if both eyes had equal Demodex mite densities, the right eye.

Following the screening visit, eligible subjects who chose to participate in the study were randomized (1:1) to receive either TP-03 or vehicle to be applied twice daily (morning and evening) in each eye for 43 days.

Following the Day 1 visit, subjects were instructed to return to the study center for efficacy and safety assessments at Days 8, 15, 22, and 43. Subjects who were active at the time of protocol version 3.0, also attended a follow-up visit 2 weeks after the last administration of study drug (Day 57). Thus, 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.

There were 421 adult (≥ 18 years) subjects with Demodex blepharitis were randomized, 287 being included in Cohort 1 (143 and 144 in the TP-03 and vehicle groups, respectively) and 134 being included in Cohort 2 (69 and 65 in the same respective groups). There were total 212 in the TP-03 group and 209 in the vehicle group. Duration of Treatment was 43 days (approximately 6 weeks).

Table 1 summarized the study objectives and efficacy endpoints for Study TRS-009.

Table 1. Study TRS-009: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the safety and efficacy of TP-03 as a cure for *Demodex* blepharitis	• Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43 • Assessment of treatment-related, treatment-emergent adverse events
Secondary	
• To demonstrate the efficacy of TP-03 in the eradication of *Demodex* mites from the eyelid margin	• Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Day 43
• To demonstrate the efficacy of TP-03 in the elimination of collarettes and erythema from the eyelid margin	• 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)
Tertiary	
• To demonstrate the efficacy of TP-03 in the reduction from baseline of the mean collarette score on the upper eyelid of the analysis eye and the mean mite density for the analysis eye at each follow-up visit	• Change from baseline in the mean collarette score for the upper eyelid of the analysis eye at Days 8, 15, 22, and 43 • Change from baseline in the mean collarette score for the upper eyelid of the analysis eye at Days 8, 15, 22, 43, and 57 (Cohort 2 only) • Change from baseline in the mean mite density for the analysis eye at Days 15, 22, and 43 • Change from baseline in the mean mite density for the analysis eye at Days 15, 22, 43, and 57 (Cohort 2 only) • Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Days 8, 15, and 22 • Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Days 8, 15, 22, 43, and 57 (Cohort 2 only) • Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 in the analysis eye at Days 15 and 22 • Proportion of subjects with eradication of *Demodex* mites in the analysis eye at Days 15, 22, 43, and 57 (Cohort 2 only) • Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Days 8, 15, and 22 • Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Days 8, 15, 22, 43, and 57 (Cohort 2 only)

The schedule of assessments for the study is presented in Table 2.

Table 2. 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: Sponsor's study report, Table 2.

Study Endpoints

See Table 1 for efficacy endpoints.

Safety*:*

- Assessment of treatment-related, treatment-emergent adverse events (TEAEs) (primary safety endpoint)
- TEAEs
- CDVA testing
- IOP measurements
- Slit-lamp biomicroscopy examinations

- Dilated fundus examinations
- Corneal fluorescein staining results
- Specular microscopy (conducted at 2 study centers)

2.3.2. Statistical Methodologies

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.

Analysis Populations

Three principal analysis sets were defined for this study: the full analysis set (FAS), the per protocol (PP) analysis set, and the safety analysis set.

- The efficacy endpoints were analyzed using the FAS, which was defined to include all randomized subjects.
- The PP analysis set was used as a sensitivity analysis of the primary efficacy endpoint, and was a subset of the FAS that included subjects (and their visits) who did not have a protocol deviation likely to affect the primary efficacy endpoint of the study as judged by a masked evaluator.
- The safety endpoints were analyzed using the safety analysis set, which was defined to include all randomized subjects who instilled study drug at least once.

Primary Estimand

Not defined but the name was mentioned once in the sponsor's study report Table 14.2.7.99.1.

Sample Size Determination

A sample size of 300 subjects (150 subjects per study drug group) yielded approximately 99% power to establish superiority of TP-03 to vehicle regard to the proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43 (the primary efficacy endpoint). The power calculation assumed response rates of 80.0% and 15.8% in the TP-03 and vehicle groups, respectively, using a Pearson chi-squared test with a 1-sided significance level of 0.025. The response rates for the sample size calculation were based on a prior clinical study (conducted outside the US) of TP-03 relative to its vehicle in the treatment of *Demodex* blepharitis.

A total of 300 subjects (150 subjects per study drug group) yielded 99% power to establish the superiority of TP-03 to vehicle in regard to both the proportion of subjects with eradication of *Demodex* based on mite density in the analysis eye at Day 43 and the proportion of subjects cured based on a composite of the collarette and erythema scores at Day 43 (i.e., the secondary efficacy endpoints). The power calculation assumed response rates of 73.3% and 21.1% in the TP-03 and vehicle groups, respectively, for the former of the secondary efficacy endpoints and response rates of 73.3% and 10.5% in the same respective groups for the latter of the secondary efficacy endpoints using a Pearson chi-squared test with a 1-sided significance level of 0.025.

Accounting for a 30% discontinuation rate, approximately 209 subjects per study drug group (approximately 418 subjects total) were planned to be randomized. The assumption of the discontinuation rate was based in part on concerns that COVID-19 could impact the ongoing participation of both individual subjects and entire study centers.

Changes in the Conduct of the Study or Planned Analyses

There were 3 notable differences between the analyses described in the approved SAP and the final revised version of the protocol. In all cases, the statistical methods and analyses presented in the SAP took precedence over similar information presented in 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. Additionally, 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.

Efficacy Analysis

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 series of sensitivity analyses was used to evaluate the robustness of the primary and secondary efficacy analyses. Specifically, 5 sensitivity analyses used different imputation methods to evaluate the primary efficacy results in the FAS, as well as to evaluate the primary efficacy results using observed data in both the FAS and the PP analysis set. Additional sensitivity analyses were performed for each of the secondary efficacy endpoints; in these analyses, missing data were imputed as failures.

Descriptive statistics were used to present results for the primary and secondary efficacy endpoints by subgroup using the FAS with observed data only. For each endpoint, the summarized subgroups consisted of sex, age category (< 65 and ≥ 65 years), and race. The results for each endpoint were also tabulated by study center.

The tertiary efficacy endpoints were analyzed using the FAS with observed data only. Changes from baseline were analyzed using an analysis of covariance model adjusted for the baseline value and with study drug group as an explanatory variable. The least squares (LS) mean values for each study drug group and the LS mean differences between study drug groups were presented along with standard errors, 2-sided p-values, and 2-sided 95% CIs. Where applicable, both the difference of proportions test and Pearson's chi-squared test (or Fisher's exact test if any of the expected cell counts were < 5) were used to assess differences between study drug groups.

Additionally, for the first 4 tertiary efficacy endpoints listed above, the differences between baseline and each subsequent visit were assessed by study drug group using a paired t-test.

Type I Error Control (Plan for Multiplicity Adjustment)

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. Specifically, if the null hypothesis was rejected at a 1-sided α of 0.025, the study was considered a success for clinical cure and the family of 2 secondary efficacy endpoints was tested using the Hochberg testing strategy with a familywise α of 0.025. If the secondary endpoint with the largest p-value was significant at the 0.025 level, then both secondary endpoints were declared significant. If the secondary endpoint with the largest p-value was not significant at the 0.025 level, then the remaining secondary endpoint was tested at the 0.0125 level. If the null hypothesis was not rejected for the primary efficacy endpoint at a 1-sided α of 0.025, the testing was stopped and both secondary efficacy endpoints were deemed not significant.

2.3.3. Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Regardless of cohort, a total of 421 subjects were enrolled into the study, including 212 (50.4%) in the TP-03 group and 209 (49.6%) in the vehicle group (Table 3). Of those subjects, 413 (98.1%) completed the Day 43 visit and 411 (97.6%) completed the study; the numbers and percentages of subjects who completed the Day 43 visit were similar in the TP-03 and vehicle groups (209 [98.6%] and 204 [97.6%], respectively), as were the numbers and percentages of subjects and who completed the study (208 [98.1%] and 203 [97.1%], respectively). Of the 10 subjects who discontinued early, the 2 most frequently reported reasons for discontinuation were COVID-19 (4 subjects, 2 in each study drug group) and TEAEs (3 subjects, 1 in the TP-03 group and 2 in the vehicle group); each of 3 other subjects discontinued for different reasons (an exclusion criterion [the subject enrolled in a study of an investigational product intended to treat COVID-19] or other [lost to follow-up or withdrawal of consent]).

Of the 421 randomized subjects, 287 (68.2%) were in Cohort 1, including 143 and 144 subjects in the TP-03 and vehicle groups, respectively, and 134 (31.8%) were in Cohort 2, including 69 and 65 subjects in the same respective groups. In Cohort 1, 279 subjects (97.2%) completed the study through Day 43. In Cohort 2, 132 subjects (98.5%) completed the study through Day 57. Thus, of the 10 subjects overall who discontinued the study, 8 were in Cohort 1 and 2 were in Cohort 2.

Table 3 shows the summary of subject disposition and the primary reasons for study discontinuation during the treatment period.

Table 3: Study TRS-009: Subject Disposition (All Randomized Subjects)

	TP-03	Vehicle	Total
Randomized, n	212	209	421
Cohort 1	143	144	287
Cohort 2	69	65	134
Completed, n (%)[a]	208 (98.1)	203 (97.1)	411 (97.6)
Cohort 1	140 (97.9)	139 (96.5)	279 (97.2)
Cohort 2	68 (98.6)	64 (98.5)	132 (98.5)
Discontinued, n (%)[a]	4 (1.9)	6 (2.9)	10 (2.4)
Reason for discontinuation, n (%)[a]			
Adverse event	1 (0.5)	2 (1.0)	3 (0.7)
Exclusion criterion	1 (0.5)	0	1 (0.2)
Reasons relating to COVID-19	2 (0.9)	2 (1.0)	4 (1.0)
Other	0	2 (1.0)[b]	2 (0.5)
Cohort 1: Discontinued, n (%)[c]	3 (1.4)	5 (2.4)	8 (1.9)
Cohort 1: Reason for discontinuation, n (%)[c]			
Adverse event	0	2 (1.4)	2 (0.7)
Exclusion criterion	1 (0.7)	0	1 (0.3)
Reasons relating to COVID-19	2 (1.4)	2 (1.4)	4 (1.4)
Other	0	1 (0.7)[d]	1 (0.3)
Cohort 2: Discontinued, n (%)[e]	1 (1.4)	1 (1.5)	2 (1.5)
Cohort 2: Reason for discontinuation, n (%)[e]			
Adverse event	1 (1.4)	0	1 (0.7)
Exclusion criterion	0	0	0
Reasons relating to COVID-19	0	0	0
Other	0	1 (1.5)[f]	1 (0.7)

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: Sponsor's study report, Table 6.

Protocol Deviations

Of the 421 subjects randomized into the study, 54 (12.8%) had at least 1 protocol deviation each (Table 4). Of those subjects, only 1, who was in the TP-03 group, had a deviation that was considered by the sponsor to be major; the deviation was related to a violation of the exclusion criteria.

Overall, 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. Note that there were no deviations associated with maintaining the study drug mask.

Table 4. Study TRS-009: Summary of Protocol Deviations (All Randomized Subjects)

	TP-03 N = 212 n (%)	Vehicle N = 209 n (%)	Total N = 421 n (%)
Any deviation	33 (15.6)	21 (10.0)	54 (12.8)
Major	1 (0.5)	0	1 (0.2)
Minor	33 (15.6)	21 (10.0)	54 (12.8)
COVID-19 related	8 (3.8)	1 (0.5)	9 (2.1)

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: Sponsor's study report, Table 7.

Analysis Population

Table 5 shows summary of the analysis populations in the study. Although only 1 subject in the TP-03 group was considered by the sponsor to have had a major protocol deviation, the masked evaluator determined that 4 subjects (3 in the TP-03 group and 1 in the vehicle group) had deviations that could have seriously affected the primary efficacy endpoint analysis; those 4 subjects were therefore excluded from the PP analysis set. The specific deviations that led to exclusion of subjects in the TP-03 group consisted of a violation of the exclusion criteria, a Day 43 visit that occurred 25 days late, and noncompliance with study drug administration (which also led to cessation of study drug use).

The specific deviation that led to exclusion of a subject in the vehicle group consisted of a Day 43 visit that occurred 10 days early. Separate from the above, 4 subjects, 2 in each study drug group, were excluded from the COVID-19 analysis set. The reason for exclusion in all 4 cases was discontinuation due to COVID-19 complications (Listing 16.2.3.2). Note that, because the difference between the numbers of subjects included in the FAS and the COVID-19 analysis sets was not $\geq 5\%$, sensitivity analyses of the primary and secondary efficacy endpoints constructed with the COVID-19 analysis set were not required.

Table 5: Study TRS-009: Analysis Sets (All Randomized Subjects)

	TP-03 N = 212 n (%)	Vehicle N = 209 n (%)	Total N = 421 n (%)
Full analysis set	212 (100.0)	209 (100.0)	421 (100.0)
Per protocol analysis set	209 (98.6)	208 (99.5)	417 (99.0)
COVID-19 analysis set	210 (99.1)	207 (99.0)	417 (99.0)
Safety analysis set	212 (100.0)	209 (100.0)	421 (100.0)

Source: Sponsor's study report, Table 8.

Demographic and Baseline Characteristics

Across study drug groups, the randomized subjects had a mean (SD) age of 67.0 (12.37) years (range = 19-94 years) (Table 6). Most subjects were female (57.0%), most were not Hispanic or Latino (94.1%), and most were White (90.7%). The majority subjects had blue or brown eyes (depending on the eye, ~41% of the subjects had a blue iris color, while ~30% of the subjects had a brown iris color). There were no notable differences between study drug groups based on demographics or iris color.

In the analysis eye at screening, a plurality of subjects in the TP-03 group had a collarette score for the upper eyelid of 2 (40.1%), while a plurality of subjects in the vehicle group had a collarette score for the upper eyelid of 3 (46.4%) (Table 10). A majority subjects in these same study drug groups had an erythema score for the upper eyelid of 1 (53.8% and 53.6%, respectively); the subjects had a similar mean (SD) mite density (3.185 [1.6735] and 3.164 [1.5947], respectively).

The demographic and baseline characteristics were tabulated by study center using the FAS and, in addition to the FAS, were tabulated using the COVID-19, PP, and safety analysis sets. No important differences in demographics or baseline characteristics were noted between analysis sets.

Table 6. 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: Sponsor's study report, Table 9.

Table 7. Study TRS-009: Collarette Score, Erythema Score, and Mite Density for the Analysis Eye at Screening (Full Analysis Set, Observed Data)

	TP-03 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: Sponsor's study report, Table 10.

2.3.4 Efficacy Results

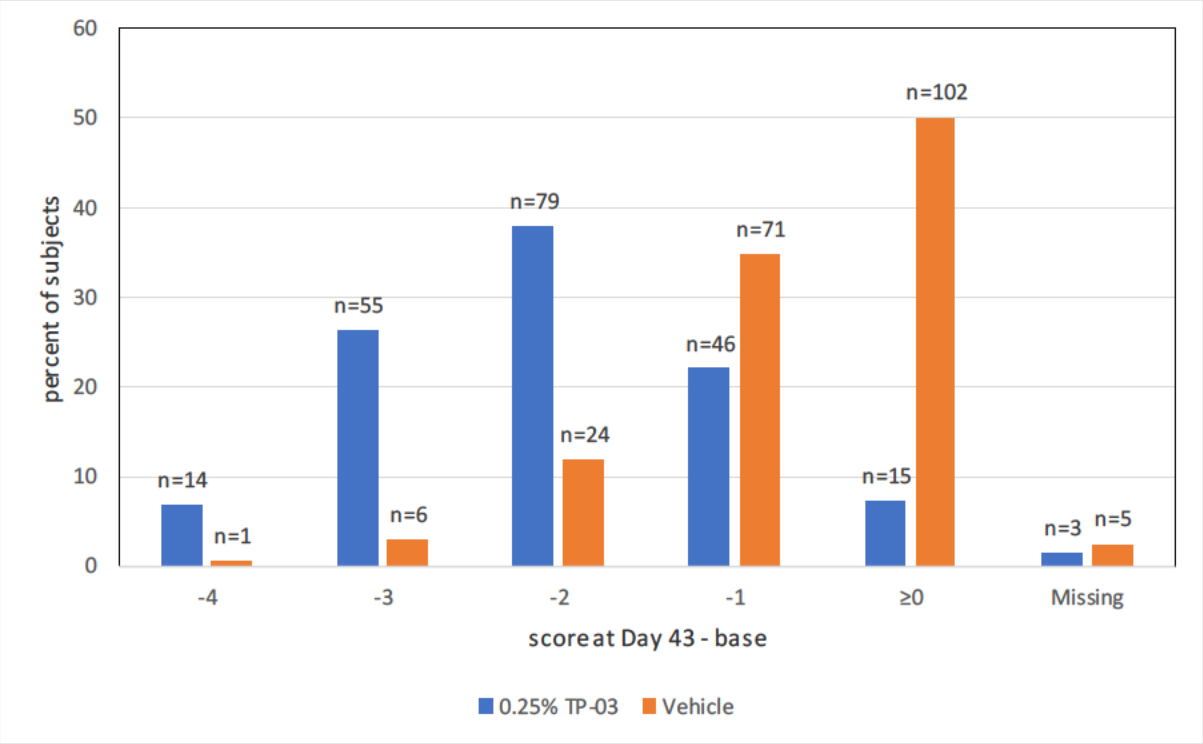
Table 8 summarized the descriptive analysis of the changes of collarette score, composite score, and erythema score (the three scores for the upper eyelid of the analysis eye), and Mite Density at Day 43 from their baselines for each treatment arm. All results showed that there are more mean reductions in the TP-03 arm than those in the vehicle arm, supporting the treatment efficacy of TP-03 at Day 43.

Table 8. Changes in Collarette Grading, Composite Score, Erythema Score, and Mite Density at Day 43 of Treatment From their Baselines (FSA population).

Parameter	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Collarette Scores (Upper Eyelid)	0.25% TP-03	209	-2.02	1.04	-4	-3	-2	-1	1
	Vehicle	204	-0.64	0.90	-4	-1	-0.5	0	1
Composite Cure (Upper Eyelid)	0.25% TP-03	209	-2.46	1.42	-6	-3	-2	-2	1
	Vehicle	204	-0.86	1.19	-5	-2	-1	0	2
Erythema Scores (Upper Eyelid)	0.25% TP-03	209	-0.44	0.75	-2	-1	0	0	1
	Vehicle	204	-0.22	0.65	-2	-1	0	0	1
Mite Density	0.25% TP-03	209	-3.06	1.65	-10	-3.75	-2.5	-1.75	-0.75
	Vehicle	204	-1.84	1.73	-10.25	-2.75	-1.5	-0.75	2.75

The number and percentage of subjects by change in collarette scores (upper eyelid of the analysis eye) between Day 43 and baseline are summarized in Figure 1. Note that the negative value of change (score at Day 43 - base) means favorable response. There were 13 subjects in the TP-03 arm with no change (no improvement) and 2 with change score of 1 (symptom worse), namely both as TP-03 treatment non-responders. The 15 non-responders in the TP-03 arm count for 7.2% (15/209) of the FAS. On the other hand, the symptom improvement in some subjects in the vehicle arm were observed. Specifically, since the collarette scores for the upper eyelid of the analysis eye were 2 to 4 at screening based on Table 7, one score reduction at Day 43 from baseline would mean approximal 25% improvement of the symptom. Accordingly, a placebo responder is defined as a subject in the vehicle arm with one or more reduction in collarette scores at Day 43 from baseline (change $\leq$ -1). Therefore, the placebo response rate of this study is 50% (102/204).

Figure 1. Percent of Subjects by Change in Collarette Scores (the Upper Eyelid of the Analysis Eye) between Day 43 and Baseline for Treatments.



Note: Percent were computed based on the number of completers for each arm, n=209 for the TP-03 arm and n=204 for the vehicle arm except for missing data based on FAS population with n=212 for TP-03 and n=209 for vehicle.

The time course of change in score from baseline for collarette score, composite score, erythema score, and mite density are shown in Figures 2 – 5. The boxplot consists of a box (the inter quantile range: IQR=Q3-Q1 with Q3=75 percentile and Q1=25 percentile), a line on each side of the box ended as the maximum (defined as Q1+1.5*IQR) and minimum (defined as Q1-1.5*IQR), and possible outliers beyond (o). The mean difference of (score - base) (the circle inside of the box) changed remarkably over treatment days for the primary and secondary endpoints where the erythema score with the smallest change. However, there are large variations for each treatment at all time points.

Figure 2: Mean Change (Score – Baseline) Over Treatment Days for Collarette Score (the Upper Eyelid of the Analysis Eye) (FAS Population)

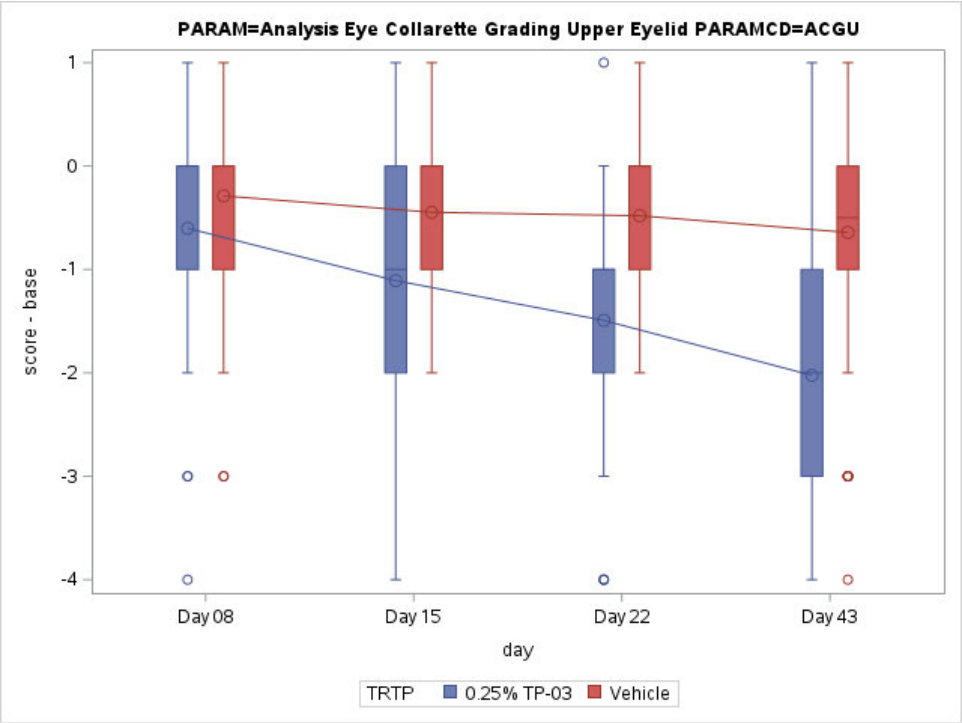


Figure 3: Mean Change (Score – Baseline) Over Treatment Days for Composite Cure (the Upper Eyelid of the Analysis Eye) (FAS Population)

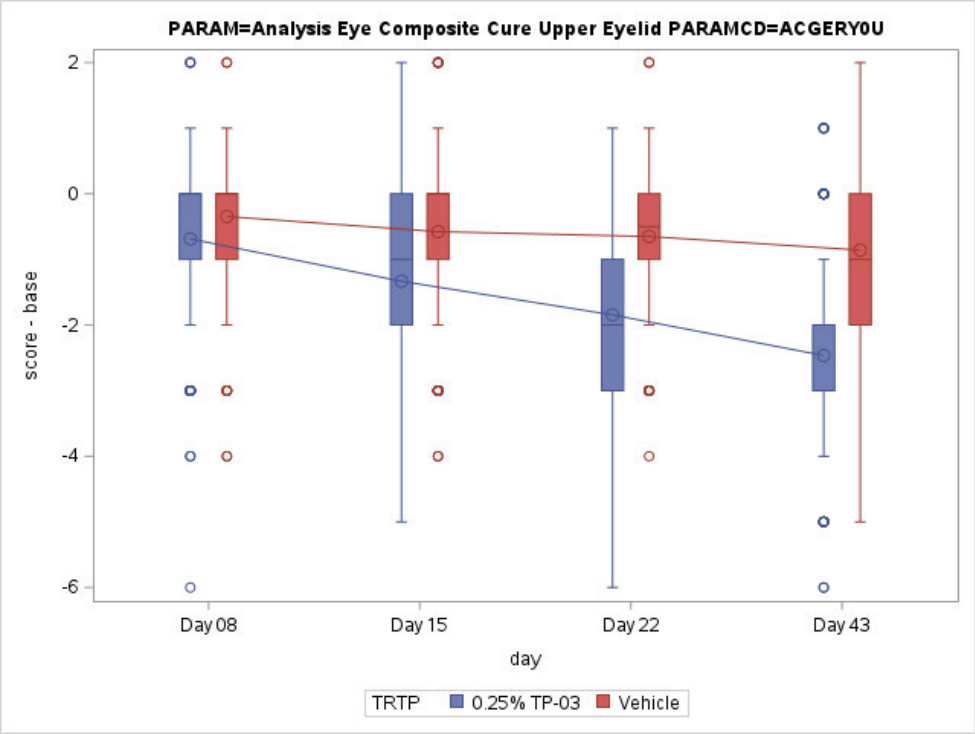


Figure 4: Mean Change (Score – Baseline) Over Treatment Days for An Erythema Score (the Upper Eyelid of the Analysis Eye) (FAS Population)

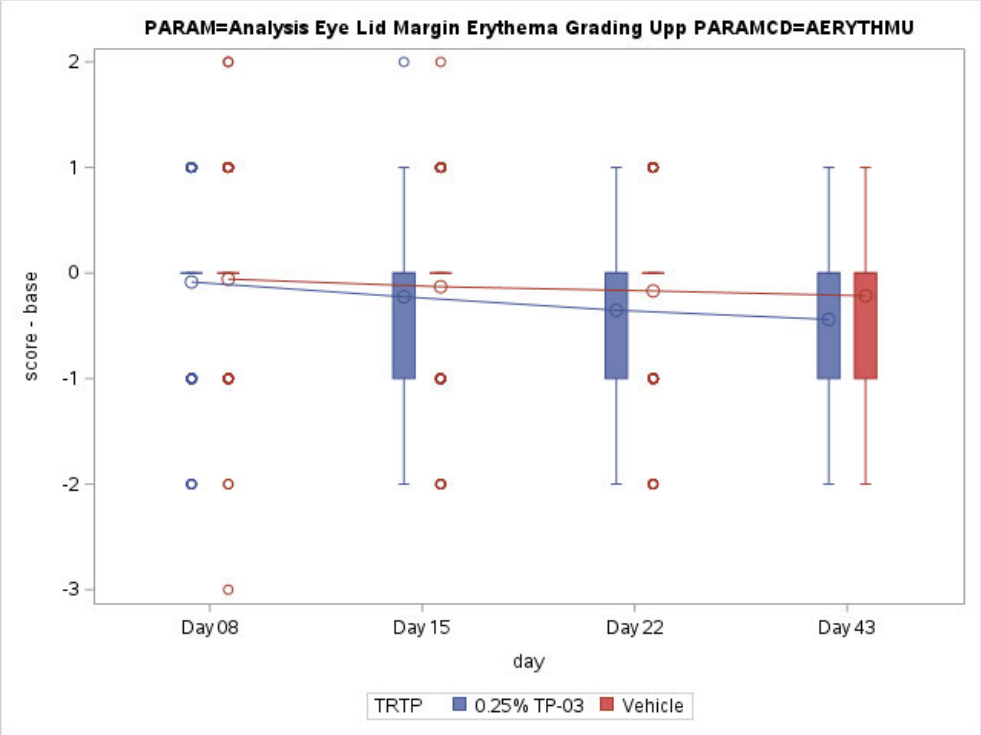
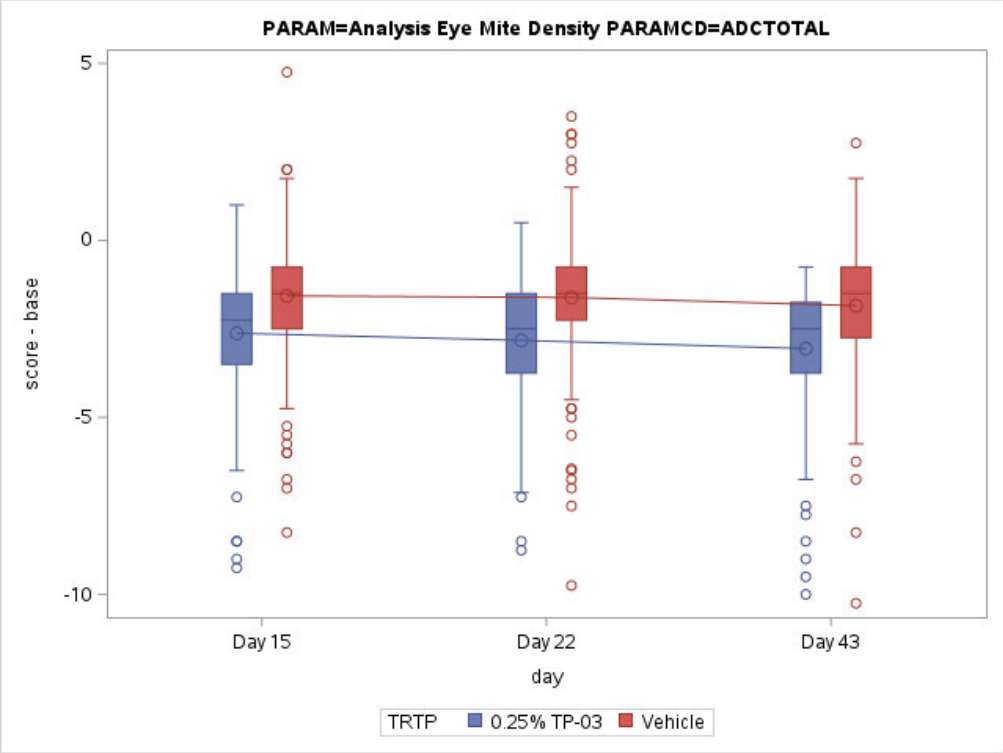


Figure 5: Mean Change (Score – Baseline) Over Treatment Days for Mite Density (FAS Population)



In the primary efficacy analysis, this reviewer verified the results by the sponsor on the primary endpoint as well as on the secondary endpoints, using the method (MCMC) proposed for dealing with missing data (see Appendix Tables 1 and 2). Since the assumptions for applying the multiple imputation based on MCMC methodology were difficult to verify, this 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. The primary analysis on the primary endpoint was shown in Tables 9, and on the secondary endpoints in Table 10, respectively. All above analyses showed that the percentage of subjects achieving a cure (score = 0) in the upper eyelid of the analysis eye at Day 43 was significantly greater in the TP-03 group than in the vehicle group (p-value < 0.0005), consistent to the sensitive analysis by the sponsor for the primary endpoint (Appendix Table 3) and for the secondary endpoints (Appendix Table 4), respectively.

Table 9. Analysis of Primary Efficacy Endpoint: Proportion of Subjects Achieving a Cure (Collarette Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (FAS Population)

	TP-03 N=212	**Vehicle N=209**
Cured (collarett score=0), n	92	15
Difference in cured, % (SE)[a]	36.2 (4.2)	
p-value[b]	<0.0001	

SE = standard error
Study dreatment discontinuation by Day 43 (missing outcomes at Day 43) were treated as treatment failure.
a The difference was computed as TP-03 minus vehicle.
b The p-value was from a difference of proportions test.

Table 10. Analysis of Secondary Endpoints: Proportion of Subjects Achieving a Cure (Score = 0) in the Upper Eyelid of the Analysis Eye at Day 43 (FAS Population)

Endpoint	**TP-03 N=212**	**Vehicle N=209**	**Difference in percent cured**
	Cured, n (%)	Cured, n (%)	Cured, % (SE) (p-value*)
Composite Cure (Upper Eyelid) score=0	29 (13.7%)	2 (1.0%)	12.7 (2.5) (<.0001)
Erythema Scores (Upper Eyelid) score=0	40 (18.9%)	14 (6.7%)	12.2 (3.2) (0.0002)
Mite Density	142 (67.0%)	36 (17.2%)	49.8(3.2) (<.0001)

* p-value from Chi-square test.

Sensitivity Analyses

This 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) seen in Table 11. These analyses were carried out on the collarett, 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.

Table 11. Sensitivity Analysis of Mean Scores for Primary and Secondary Endpoints. All Missing Data Were Imputed as Treatment Failures (FAS Population)

Endpoint	TP-03 N=212	Vehicle N=209	Difference
	Mean (SE)	Mean (SE)	Mean diff (SE) (p-value*)
Collarett (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 TP-03, 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, this reviewer verified the sponsor's descriptive subgroup analysis of subjects achieving a cure at Day 43 as shown in Table 12 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 TP-03 relative to that for vehicle in subgroups with reasonable sample sizes.

Table 12. Study TRS-009: Subgroup Summaries of the Primary Efficacy Endpoint (Observed Data, Full Analysis Set)

	TP-03 N = 212	Vehicle N = 209
Sex, n/N (% [SE])		
Female	57/120 (47.5 [4.6])	9/114 (7.9 [2.5])
Male	35/89 (39.3 [5.2])	6/90 (6.7 [2.6])
Age, n/N (% [SE])		
< 65 years	41/86 (47.7 [5.4])	4/62 (6.5 [3.1])
≥ 65 years	51/123 (41.5 [4.4])	11/142 (7.7 [2.2])
Race, n/N (% [SE])		
American Indian or Alaska Native	0/1 (0)	0/1 (0)
Asian	1/3 (33.3 [27.2])	0/2 (0)
Black or African American	5/10 (50.0 [15.8])	0/14 (0)
Multiple	2/2 (100.0 [0.0])	1/3 (33.3 [27.2])
White	84/193 (43.5 [3.6])	14/184 (7.6 [2.0])

SE = standard error
The primary efficacy endpoint was the proportion of subjects achieving a cure (collarette score = 0) in the upper eyelid of the analysis eye at Day 43. Percentages are based on the total number of subjects in each respective study drug group within each age group, sex, and race using observed data only with nonmissing data at each time point.
Source: Sponsor's study report, Table 14.

2.3.5 Efficacy Summary for Study TRS-009 (SATURN-1)

The data of Study TRS-009 (SATURN-1) were supportive to demonstrate the efficacy of TP-03 in the treatment of *Demodex* blepharitis for 43 days. A significantly greater percentage of subjects in the TP-03 group achieved a cure (i.e., collarette score = 0) as well as a composite cure (i.e., collarette and erythema scores of 0) and erythema cure (i.e., erythema score = 0) in the upper eyelid of the analysis eye, and an eradication of *Demodex* mites (i.e., mite density = 0) in the analysis eye at Day 43 relative to those in the vehicle group at the level of 0.05.

However, the overall percentage of cured subjects relative to vehicle treatment, based on the primary endpoint, is less than 40%. This reviewer also noted that there were 15 (7%) randomized subjects being TP-03 treatment non-responders that at Day 43 the collarette grading scores in the upper eyelid of the analysis eye of these subjects either remained the same as, or were even higher (symptom worse) than, their baseline levels.

2.4. STUDY TRS-010 (SATURN-2)

2.4.1. Study Design and Endpoints

This Phase 3 study was designed basically identical to the Phase 2b/3 Study SATURN-1, with a main change of an additional secondary efficacy endpoint, erythema score of zero for the upper eyelid of the analysis eye at Day 43 as seen in Table 13.

Table 13. Study TRS-010: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the safety and efficacy of TP-03 as a cure for *Demodex* blepharitis	• Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43 • The assessment of treatment-related adverse events
Secondary	
• To demonstrate the efficacy of TP-03 in the eradication of *Demodex* mites from the eyelid margin	• Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0 per lash in the analysis eye at Day 43
• To demonstrate the efficacy of TP-03 in the elimination of collarettes and erythema from the eyelid margin	• 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)
• To demonstrate the efficacy of TP-03 in the elimination of erythema from the eyelid margin	• Proportion of subjects cured based on erythema scores of 0 for the upper eyelid of the analysis eye at Day 43
Tertiary	
• To demonstrate the efficacy of TP-03 in the reduction from baseline of the collarette score and erythema score for the upper eyelid of the analysis eye and the mite density on the upper eyelid of the analysis eye at each follow-up visit	• Change from baseline in the collarette score for the upper eyelid of the analysis eye at each follow-up visit • Change from baseline in the mite density for the analysis eye at each follow-up visit • Change from baseline in the erythema score for the upper eyelid of the analysis eye at each follow-up visit
• To evaluate the time course of cure, *Demodex* mite eradication, composite cure, and erythema cure	• Proportion of subjects cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Days 8, 15, and 22
	• Proportion of subjects with eradication of *Demodex* mites based on a mite density of 0/lash in the analysis eye at Days 15 and 22 • Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Days 8, 15, and 22 • Proportion of subjects cured based on an erythema score of 0 for the upper eyelid of the analysis eye at Days 8, 15, and 22

The schedule of assessments for the study is presented in Table 14.

Table 14. Study TRS-010: 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	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.

2.4.2. Statistical Methodologies

The planned statistical methodologies were basically identical to those in the Phase 2b/3 Study SATURN-1.

Changes in the Conduct of the Study or Planned Analyses

There was only one minor difference between the analyses described in the approved SAP and the final revised version of the protocol for the dosing compliance calculation. The SAP specified the number of expected doses as 2 × (Date of Last Dose – Date of First Dose) + 1 regardless of study completion status. The final analysis methodology accounted for the study completion status and calculated expected number of doses as follows:

• 2 × (Date of Last Diary Entry – Date of First Dose) + 1 for all subjects who were enrolled in the study through the Day 43 visit (even if missed Day 43 visit), or for subjects who discontinued the study before the Day 43 visit and whose last diary entry was in the morning

• 2 × (Date of Last Dose – Date of First Dose) + 1 for subjects who discontinued the study before the Day 43 visits and for who the diary was not filled or collected

• 2 × [(Date of Last Diary entry – Date of First Dose) + 1] for subjects who discontinued the study before the Day 43 visit and whose last diary entry was in the evening

The SAP also stated that "In the case where drug was temporarily withdrawn, the number of days without study drug will be accounted for by subtracting 2 doses per day without study drug". However, since the dates of temporary withdrawal of study drug were not collected, the dosing compliance assessment does not account for temporary withdrawal of study drug.

2.4.3. Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 412 subjects were enrolled into the study, including 203 (49.3%) in the TP-03 group and 209 (50.7%) in the vehicle group (Table 16). Of those 412 subjects, 393 (95.4%) have completed through the last planned efficacy assessment visit (either Day 57 for subjects in Cohort 1 or Day 43 for subjects in Cohort 2) and 19 (4.6%) have discontinued. The numbers and percentages of subjects who completed the study were similar in the TP-03 and vehicle groups (36 [17.7%] and 37 [17.7%], respectively). Of the 19 subjects who discontinued early, the 2 reported reasons for discontinuation were AE (3 subjects: 2 in the TP-03 group and 1 in the vehicle group) and Other (16 subjects: 8 subjects in the TP-03 group and 8 subjects in the vehicle group). Of the 393 subjects who completed the last efficacy assessment at either Day 43 or 57, as applicable by cohort, 73 completed the study and 320 are ongoing with a final safety follow-up visit to be conducted at Day 90.

Of the 412 randomized subjects, 265 (64.3%) were in Cohort 1, including 131 and 134 subjects in the TP-03 and vehicle groups, respectively, and 147 (35.7%) were in Cohort 2, including 72 and 75 subjects in the same respective groups.

Table 15 shows the summary of subject disposition and the primary reasons for study discontinuation during the treatment period.

Table 15: Study TRS-010: Subject Disposition (All Randomized Subjects)

	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 in the sponsor's study report.
Source: Sponsor's study report, Table 6.

Protocol Deviations

Of the 412 subjects randomized into the study, 236 (57.3%) had at least 1 protocol deviation each (Table 16). Of those subjects, 12 subjects (7 in the TP-03 group and 5 in the vehicle group) had a deviation that was considered by the sponsor to be major; 5 deviations were related to violations of inclusion/exclusion criteria, 3 deviations were related to improper protocol procedures at the study center, 2 deviations were related to noncompliance with study drug, 1 deviation was related to study drug assignment at the study center, and 1 deviation was related to a visit out of the window (Listing 16.2.2). Protocol deviations that resulted in the exclusion of a subject from any of the analysis sets are described in Section 8.3. Of these major protocol deviations, those related to inclusion/exclusion criteria, noncompliance with study drug, and visit out of the window were considered to have a potential impact on the primary efficacy endpoint.

Overall, 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%]), and other (6 subjects total [1.5%]) (Table 14.1.1). These deviations occurred in similar numbers of subjects in each study drug group. Note that there were no deviations associated with maintaining the study drug mask.

Table 16. Study TRS-010: Summary of Protocol Deviations (All Randomized Subjects)

	TP-03 N = 203 n (%)	Vehicle N = 209 n (%)	Total N = 412 n (%)
Any deviation	113 (55.7)	123 (58.9)	236 (57.3)
Major	7 (3.4)	5 (2.4)	12 (2.9)
Minor	111 (54.7)	121 (57.9)	232 (56.3)
COVID-19 related	2 (1.0)	3 (1.4)	5 (1.2)

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: Sponsor's study report, Table 7.

Analysis Population

Table 17 shows summary of the analysis populations in the study. Although only 1 subject in the TP-03 group was considered by the sponsor to have had a major protocol deviation, the masked evaluator determined that 4 subjects (3 in the TP-03 group and 1 in the vehicle group) had deviations that could have seriously affected the primary efficacy endpoint analysis; those 4 subjects were therefore excluded from the PP analysis set. The specific deviations that led to exclusion of subjects in the TP-03 group consisted of a violation of the exclusion criteria, a Day 43 visit that occurred 25 days late, and noncompliance with study drug administration (which also led to cessation of study drug use).

The specific deviation that led to exclusion of a subject in the vehicle group consisted of a Day 43 visit that occurred 10 days early. Separate from the above, 4 subjects, 2 in each study drug group, were excluded from the COVID-19 analysis set. The reason for exclusion in all 4 cases was discontinuation due to COVID-19 complications (Listing 16.2.3.2). Note that, because the difference between the numbers of subjects included in the FAS and the COVID-19 analysis sets was not ≥ 5%, sensitivity analyses of the primary and secondary efficacy endpoints constructed with the COVID-19 analysis set were not required.

Table 17: Study TRS-010: Analysis Sets (All Randomized Subjects)

	TP-03 N = 203 n (%)	Vehicle N = 209 n (%)	Total N = 412 n (%)
Full analysis set	203 (100.0)	209 (100.0)	412 (100.0)
COVID-19 analysis set	203 (100.0)	209 (100.0)	412 (100.0)
Per protocol analysis set	197 (97.0)	202 (96.7)	399 (96.8)
Safety analysis set	203 (100.0)	209 (100.0)	412 (100.0)

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: Sponsor's study report, Table 8.

Demographic and Baseline Characteristics

Across study drug groups, the randomized subjects had a mean (SD) age of 64.5 (14.26) years (range = 18-89 years) (Table 18). Most subjects were male (51.5%), most were not Hispanic or Latino (91.7%), and most were White (88.1%). The majority of subjects had blue or brown eyes (29.1% of the subjects had a blue iris color, and 43.0% of the subjects had a brown iris color). There were no notable differences between study drug groups based on demographics or iris color.

Table 18. Study TRS-010: Demographics (Full Analysis Set)

	TP-03 N = 203	Vehicle N = 209	Total N = 412
Age			
Mean (SD)	63.9 (15.15)	65.1 (13.35)	64.5 (14.26)
Min, max	18, 88	24, 89	18, 89
< 65 years, n (%)	84 (41.4)	80 (38.3)	164 (39.8)
≥ 65 years, n (%)	119 (58.6)	129 (61.7)	248 (60.2)

Sex, n (%)			
Male	106 (52.2)	106 (50.7)	212 (51.5)
Female	97 (47.8)	103 (49.3)	200 (48.5)
Childbearing Potential, n (%)[a]			
Yes	10 (10.3)	8 (7.8)	18 (9.0)
No	87 (89.7)	95 (92.2)	182 (91.0)
Ethnicity, n (%)			
Hispanic or Latino	17 (8.4)	17 (8.1)	34 (8.3)
Not Hispanic or Latino	186 (91.6)	192 (91.9)	378 (91.7)
Race, n (%)			
American Indian or Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Asian	3 (1.5)	3 (1.4)	6 (1.5)
Black or African American	20 (9.9)	15 (7.2)	35 (8.5)
Native Hawaiian or Other Pacific Islander	2 (1.0)	0	2 (0.5)
White	176 (86.7)	187 (89.5)	363 (88.1)
Other	0	3 (1.4)	3 (0.7)
Multiple Race	1 (0.5)	0	1 (0.2)

max = maximum; min = minimum; SD = standard deviation
a Percentages were based on the number of female subjects.
Source: Sponsor's study report, Table 9.

In the analysis eye at screening, the majority of subjects in both the TP-03 and vehicle groups had a collarette score for the upper eyelid of 3 (39.4% and 36.8%, respectively) (Table 19). A majority of subjects in these same study drug groups had an erythema score for the upper eyelid of 1 (52.7% and 47.4%, respectively); the subjects had a similar mean (SD) mite density (3.161 [1.4217] and 3.333 [1.7061], respectively).

The demographics were tabulated by study center using the FAS and, in addition to the FAS, were tabulated using the COVID-19, PP, and safety analysis sets. No important differences in demographics were noted between analysis sets.

Table 19. 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 (35.5)	64 (30.6)
3	80 (39.4)	77 (36.8)
4	51 (25.1)	68 (32.5)
Erythema score (upper eyelid), n (%)[b]		
1	107 (52.7)	99 (47.4)
2	80 (39.4)	94 (45.0)
3	16 (7.9)	16 (7.7)
Mite density[c]		
Mean (SD)	3.161 (1.4217)	3.333 (1.7061)
Median	2.750	3.000
Min, max	1.50, 8.75	0.50, 10.00

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: Sponsor's study report, Table 10.

2.4.4. Efficacy Results

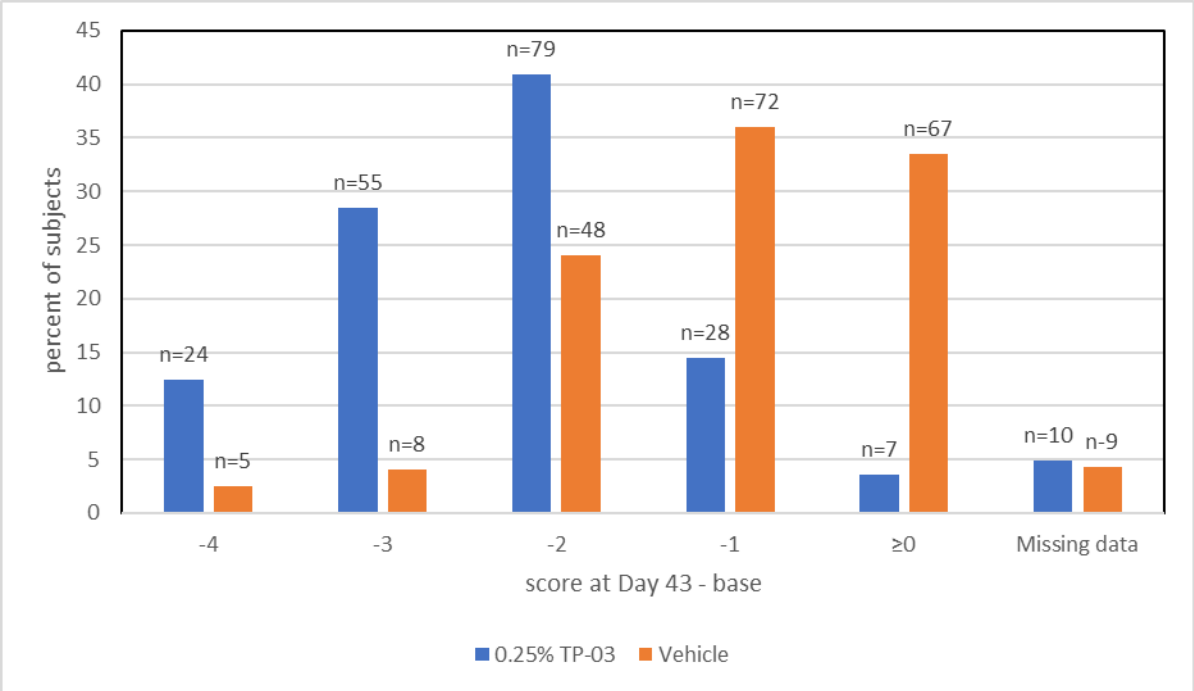
Table 20 summarized the descriptive analysis for the changes of collarette score, composite score, and erythema score (the three scores for upper eyelid of the analysis eye), and Mite Density at Day 43 of treatment from their baselines (completers) for each treatment arm. All results showed that there are more mean reductions in the TP-03 arm than that in the vehicle arm, supporting the treatment efficacy of TP-03 at Day 43.

Table 20. Changes in Collarette Grading, Composite Score, Erythema Score, and Mite Density at Day 43 of Treatment From their Baselines.

Parameter	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Collarette Scores (Upper Eyelid)	0.25% TP-03	193	-2.20	1.09	-4	-3	-2	-2	0
	Vehicle	200	-0.99	1.03	-4	-2	-1	0	1
Composite Cure (Upper Eyelid)	0.25% TP-03	193	-2.78	1.43	-6	-4	-3	-2	0
	Vehicle	200	-1.28	1.45	-6	-2	-1	0	2
Erythema Scores (Upper Eyelid)	0.25% TP-03	193	-0.49	0.78	-2	-1	-1	0	1
	Vehicle	200	-0.27	0.70	-3	-1	0	0	2
Mite Density	0.25% TP-03	193	-2.74	1.56	-8.75	-3.6	-2.5	-1.75	0.25
	Vehicle	199	-1.85	2.01	-9	-2.85	-1.5	-0.5	3.65

The number and percentage of subjects by change in collarette scores between Day 43 and baseline are shown in Figure 6. There were 7 non-responders in the TP-03 arm counting for 3.3% (7/209). The placebo response rate (with reduction in the collarette scores at least one score, i.e., change ≤ -1 for the upper eyelid of the analysis eye) of this study is 63.6% (133/209).

Figure 6. Percent of Subjects by Change in Collarette Scores (Upper Eyelid of the Analysis Eye) between Day 43 and Baseline for Treatments.



Percent were computed based on the number of completers for each arm, n=193 for TP-03 arm and n=200 for vehicle arm except for missing data based on FAS population with n=203 for TP-03 and n=209 for vehicle.

The time course of changes from baseline for the collarette score, the composite score, and erythema score, and mite density are shown in Figures 7 – 10. The mean difference of (score - base) (the circle inside of the box) changed remarkably over treatment days for the primary and secondary endpoints where the erythema score with the smallest change. However, there are large variations for each treatment at all time points.

Figure 7: Mean Change (Score – Baseline) Over Treatment Days for Collarette Score (Upper Eyelid of the Analysis Eye)

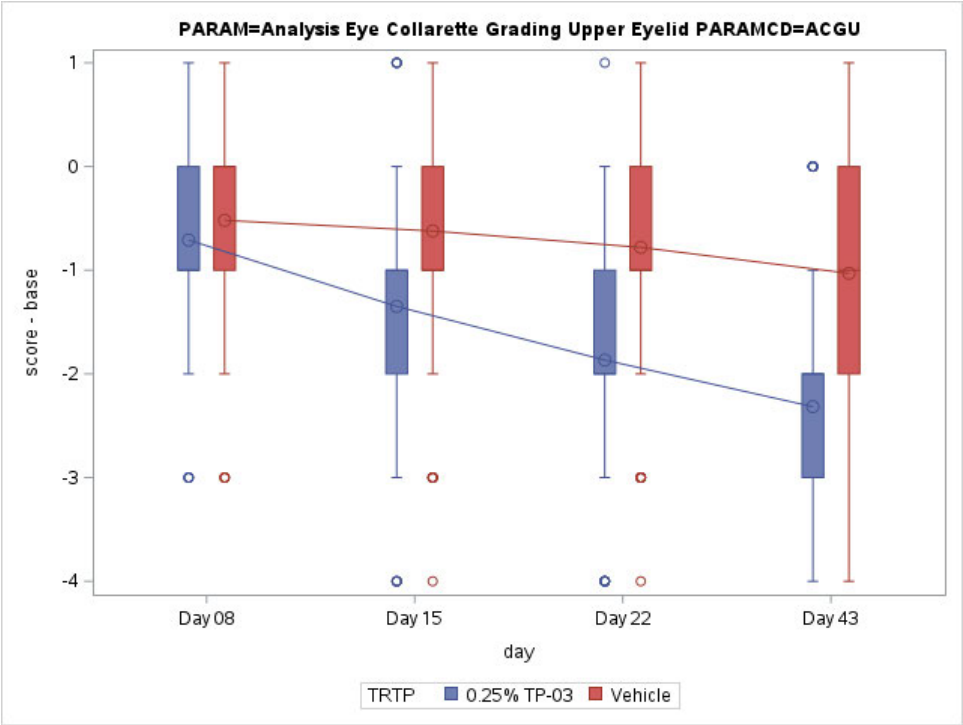


Figure 8: Mean Change (Score – Baseline) Over Treatment Days for Composite Cure (Upper Eyelid of the Analysis Eye)

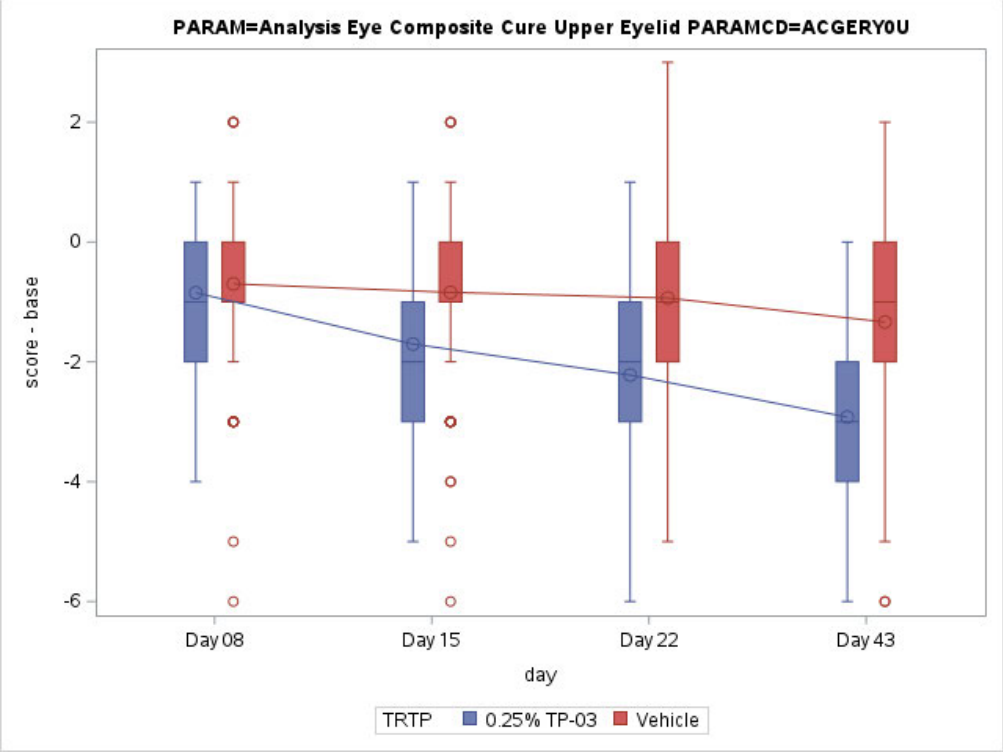


Figure 9: Mean Change (Score – Baseline) Over Treatment Days for An Erythema Score (Upper Eyelid of the Analysis Eye)

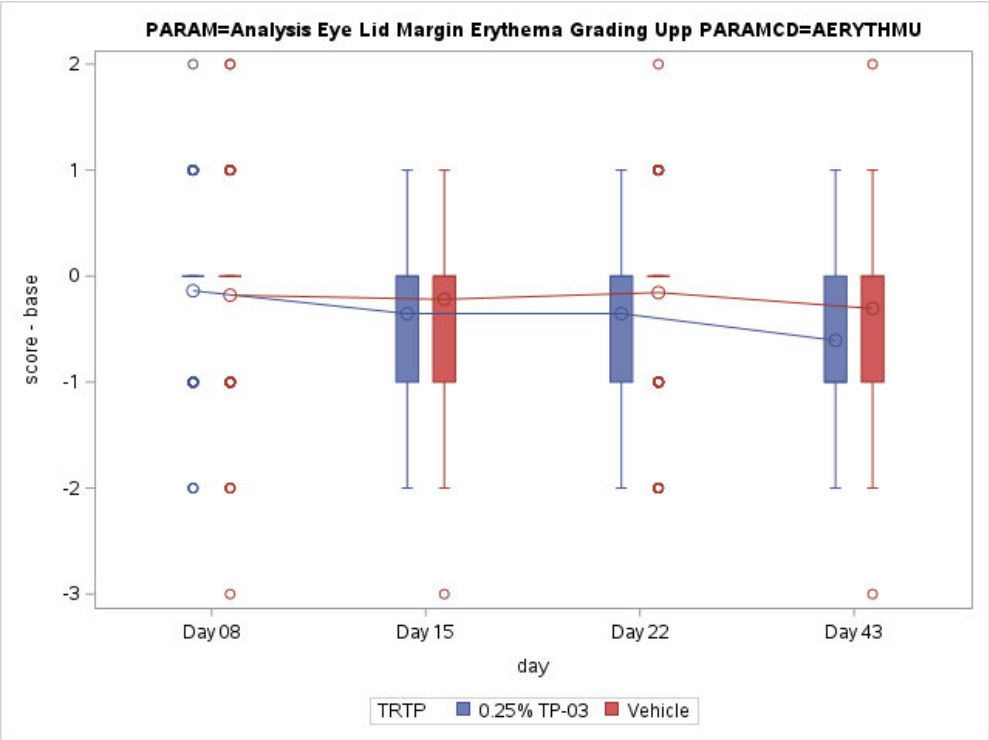
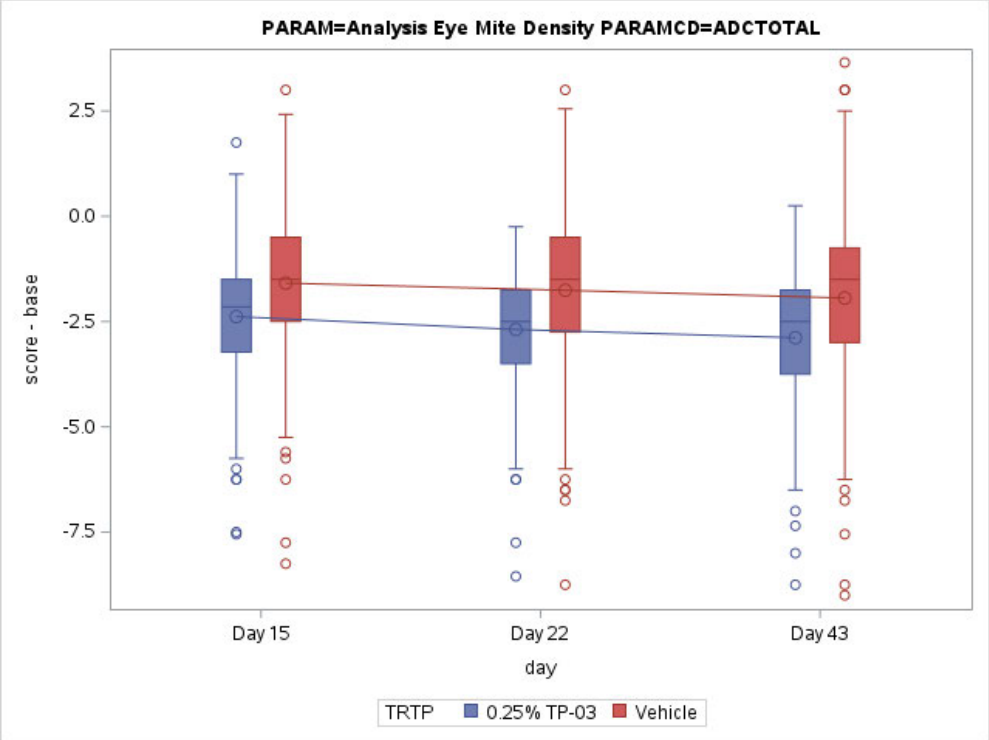


Figure 10: Mean Change (Score – Baseline) Over Treatment Days for Mite Density



The results of the primary analysis by the sponsor on the primary endpoint as well as on the secondary endpoints (see Appendix Tables 5 and 6), using the method (MCMC) proposed for dealing with missing data, were verified by this reviewer. As done for the Study TRS-009, this reviewer's efficacy analysis treated the treatment discontinuation by Day 43 (missing outcomes at Day 43) as treatment failure. The primary analysis on the primary endpoint was shown in Tables 21, and on the secondary endpoints in Table 22, respectively. All above analyses showed that the percentage of subjects achieving a cure (score = 0) in the upper eyelid of the analysis eye at Day 43 was significantly greater in the TP-03 group than in the vehicle group (p-value < 0.0001), consistent to the sensitive analysis by the sponsor for the primary endpoint (Appendix Table 7) and for the secondary endpoints (Appendix Table 8), respectively.

Table 21. 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 (Randomized Population)

	TP-03 N=203	**Vehicle N=209**
Cured (collarett score=0), n (%)	108 (53.2%)	25 (12.0%)
Difference in cured, % (SE)[a]	41.2 (4.2)	
p-value[b]	<.0001	

Sensitivity Analyses

This 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) seen in Table 22. These analyses were carried out on the collarett, 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.

Table 22. Sensitivity Analysis of Cured Percentage for Primary and Secondary Endpoints. All missing data were imputed as failures (FAS Population)

Endpoint	**TP-03 N=203**	**Vehicle N=209**	**Difference in percent cured**
	Cured,n (%)	Cured,n (%)	Cured, % (SE) (p-value*)
Composite Cure (Upper Eyelid) score=0	37 (18.2%)	8 (3.8%)	14.4 (3.0) (<.0001)
Erythema Scores (Upper Eyelid) score=0	60 (29.6%)	18 (8.6%)	20.9 (3.7) (<.0001)
Mite Density	100 (49.3%)	29 (13.9%)	35.4 (4.6) (<.0001)

* p-value from Chi-square test.

Table 23. Sensitivity Analysis of Mean Scores for Primary and Secondary Endpoints. All missing data were imputed as failures (FAS Population)

Endpoint	TP-03 N=203	Vehicle N=209	Difference
	Mean (SE)	Mean (SE)	Mean diff (SE) (p-value*)
Collarett (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

As for the design of the Study TRS-090, 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, this reviewer verified the sponsor's descriptive subgroup analysis of subjects achieving a cure at Day 43 as shown in Table 24 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 TP-03 relative to that of vehicle in subgroups consistently.

Table 24. Study TRS-010: Subgroup Summaries of the Primary Efficacy Endpoint (Observed Data, Full Analysis Set)

	TP-03 N = 203	Vehicle N = 209
Sex, n/N (% [SE])		
Female	53/91 (58.2 [5.2])	14/100 (14.0 [3.5])
Male	55/102 (53.9 [4.9])	11/100 (11.0 [3.1])
Age, n/N (% [SE])		
< 65 years	47/78 (60.3 [5.5])	14/74 (18.9 [4.6])
≥ 65 years	61/115 (53.0 [4.7])	11/126 (8.7 [2.5])
Race, n/N (% [SE])		
Non-White	9/26 (34.6 [9.3])	5/21 (23.8 [9.3])
White	99/167 (59.3 [3.8])	20/179 (11.2 [2.4])

SE = standard error

The primary efficacy endpoint was the proportion of subjects achieving a cure (collarette score = 0) in the upper eyelid of the analysis eye at Day 43.

Percentages are based on the total number of subjects in each respective study drug group within each age group, sex, and race using observed data only with nonmissing data at each time point.

Source: Sponsor's study report, Table 14.

2.4.5. Efficacy Summary for Study TRS-010 (SATURN-2):

The data of Study TRS-010 (SATURN-2) were supportive to demonstrate the efficacy of TP-03 in the treatment of *Demodex* blepharitis for 43 days. A significantly greater percentage of subjects in the TP-03 group achieved a cure (i.e., collarette score = 0) as well as a composite cure (i.e., collarette and erythema scores of 0) and an erythema cure (i.e., erythema score = 0) in the

upper eyelid of the analysis eye, and an eradication of *Demodex* mites (i.e., mite density = 0) in the analysis eye at Day 43 relative to those in the vehicle group at the level of 0.05.

However, the overall percentage of cured subjects relative to vehicle treatment, based on the primary endpoint, is less than 50%. This reviewer also noted that there were 7 (3.4%) randomized subjects being TP-03 non-responders that at Day 43 the collarette grading scores in the upper eyelid of the analysis eye of these subjects remained the same as their baseline levels.

2.5. FINDINGS IN SPECIAL/SUBGROUP

In each of the two studies, Study TRS-009 and Study TRS-010, the randomization of subjects into the TP-03 and vehicle arms were not stratified by the collarett scores (upper eyelid) at screening. As a result, a plurality of subjects in the TP-03 group had a collarette score of 2 (40.1%), while a plurality of subjects in the vehicle group had a collarette score of 3 (46.4%) in the Study 009. For the Study 010, the percentage of subjects a collarette score for the upper eyelid of 2 at screening was 35.5% in the TP-03 group, and 30.6% in the vehicle groups, respectively. To check the possible effects of the appearing unbalanced baseline scores on the TP-03 treatment, the percentage of cured subjects (collarette score=0 for the upper eyelid) respect to the total randomized subjects in each score level at screening for each arm at Day 43 was computed as summarized in Table 25. In both studies, the largest percentage of cured subjects in each arm was found in those with collarette score of 2 at screening. It appears that subjects with a lower Collarett Score (Upper Eyelid) at screening will be cured by TP-03 treatment more effectively, as seen for Study TRS-009 and Study TRS-010, 52.9% and 63.9% of subjects with a score of 2 at screening were cured by TP-03 at Day 43, respectively.

Table 25. Percentage of Cured Subjects with Different Collarett Scores (Upper Eyelid) at Screening by Treatment at Day 43.

Scores	Randomization		Day 43Cured[a]	
	TP-03, N	Vehicle, N	TP-03 (n/N), %	Vehicle (n/N), %
TRS-009: N=212 (TP-03) N=209 (vehicle)				
2	85	74	(45/85) 52.9%	(10/74) 4.8%
3	80	97	(33/80) 41.3%	(4/97) 4.1%
4	47	38	(14/47) 29.8%	(1/38) 2.6%
TRS-010: N=203 (TP-03), N=209 (vehicle)				
2	72	64	(46/72) 63.9%	(15/64) 23.4%
3	80	77	(38/80) 47.5%	(5/77) 6.5%
4	51	68	(24/51) 47.1%	(5/68) 7.4%

a All missing values were imputed as treatment failures

3. SUMMARY AND CONCLUSIONS

3.1. STATISTICAL ISSUES

There were subjects who were TP-03 non-responders that at Day 43 the collarette grading scores in the upper eyelid of the analysis eye in data of both studies with n=15 (7%) in Study TRS-009 (SATURN-1) and n=7 (3.4%) in Study TRS-010 (SATURN-2), respectively.

There are no other major statistical issues that may limit the analysis in the submission.

3.2. COLLECTIVE EVIDENCE

Collective evidence to support the efficacy and safety of TP-03 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 (b) (4) in the treatment of Demodex.

3.3. CONCLUSION AND RECOMMENDATION

Based on the collective efficacy evidence from the two pivotal studies, the reviewer concludes that the data of the two pivotal studies, TRS-009 (SATURN-1) and TRS-010 (SATURN-2), provided substantial evidence to demonstrate a favorable treatment effect of TP-03 relative to that of vehicle in the treatment of *Demodex* blepharitis for 43 days. A significantly greater percentage of subjects in the TP-03 group achieved a cure (i.e., collarette score = 0) as well as a composite cure (i.e., collarette and erythema scores of 0) and an eradication of *Demodex* mites (i.e., mite density = 0) in the upper eyelid of the analysis eye at Day 43 relative to those in the vehicle group at a level of alpha 0.05.

Overall, this reviewer concluded that the data of the two pivotal studies provided substantial evidence for TP-03 efficacy benefit, applied twice daily (morning and evening) in each eye for 43 days, in the treatment of *Demodex* blepharitis.

3. Labeling Recommendation

In the proposed label, the table and figures for efficacy should be based on all randomized patients by viewing the subjects of treatment discontinuation by Day 43 (missing outcomes at Day 43) as treatment failure because the main reason for study discontinuation is either AE or COVID-19. The two studies should be presented separately.

Appendix:

Study 009

Table 1. Analysis of 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 = 212	Vehicle N = 209
Cured (collarette score = 0), % (SE)	43.9 (3.4)	7.2 (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: Sponsor's study report, Table 12.

Table 2. Study TRS-009: Analyses of the Secondary Efficacy Endpoint – 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)

	TP-03 N = 212	Vehicle N = 209
Eradication of *Demodex* mites		
Cured (mite density = 0), % (SE)	67.7 (3.2)	17.3 (2.6)
Difference in proportion cured (SE)[a]	0.5046 (0.0416)	
p-value[b]	< 0.0001	
Composite cure		
Cured (collarette and erythema scores = 0), % (SE)	13.9 (2.4)	1.0 (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: Sponsor's study report, Table 15.

Table 3. Study TRS-009: Sensitivity Analyses of the Primary Efficacy Endpoint (Full Analysis Set or Per Protocol Analysis Set, as Specified)

	TP-03 N = 212	Vehicle N = 209
Sensitivity analysis 1 (FAS with imputations for missing data)[a]		
Cured (collarette score = 0), % (SE)	43.4 (3.4)	7.4 (1.8)
Difference in proportion cured (SE)	0.3596 (0.0387)	
p-value[b]	< 0.0001	
Sensitivity analysis 2 (FAS with imputations for missing data)[c]		
Cured (collarette score = 0), % (SE)	43.9 (3.4)	7.5 (1.8)
Difference in proportion cured (SE)	0.3643 (0.0388)	
p-value[b]	< 0.0001	
Sensitivity analysis 3 (PP analysis set with observed data)[d]		
Cured (collarette score = 0), n/N (% [SE])	91/207 (44.0 [3.4])	15/203 (7.4 [1.8])
Difference in proportion cured (SE)	0.3657 (0.0391)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	
Sensitivity analysis 4 (FAS with observed data)[f]		
Cured (collarette score = 0), n/N (% [SE])	92/209 (44.0 [3.4])	15/204 (7.4 [1.8])
Difference in proportion cured (SE)	0.3667 (0.0389)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	
Sensitivity analysis 5 (FAS with imputations for missing data)[g]		
Cured (collarette score = 0), % (SE)	43.4 (3.4)	7.2 (1.8)
Difference in proportion cured (SE)	0.3622 (0.0384)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	

FAS = full analysis set; PP = per protocol analysis set; SE = standard error
The primary efficacy endpoint was the proportion of subjects achieving a cure (collarette score = 0) in the upper eyelid of the analysis eye at Day 43.
Differences between study drug groups were calculated as TP-03 minus vehicle.
a Missing data were imputed assuming they were not missing at random (i.e., imputing from the vehicle group), with the analysis based on the FAS. Multiple imputation datasets were used to calculate cure based on a collarette score of 0 at Day 43.
b The p-value was from a difference of proportions test.
c Missing data were imputed assuming they were missing at random (i.e., imputing from the same study drug group as the subject with the missing data), with the analysis based on the FAS. The multiple imputation datasets were used to calculate cure based on a collarette score of 0 at Day 43.
d Using observed data at Day 43 in the per protocol analysis set, N = 207 for the TP-03 group and N = 203 for the vehicle group.
e The p-value was based on Pearson's chi-squared test (or Fisher's exact test if any of the expected cell counts were < 5).
f Using observed data at Day 43 in the FAS, N = 209 for the TP-03 group and N = 204 for the vehicle group.
g All missing data were imputed as failures.
Source: Sponsor's study report, Table 13.

Table 4. Study TRS-009: Sensitivity Analyses of the Secondary Efficacy Endpoints (Full Analysis Set)

	TP-03 N = 212	Vehicle N = 209
Eradication of *Demodex* mites[a]		
Cured (mite density = 0), % (SE)	67.0 (3.2)	17.2 (2.6)
Difference in proportion cured (SE)[b]	0.4976 (0.0415)	
p-value[c]	< 0.0001	
p-value[d]	< 0.0001	
Composite cure[a]		
Cured (collarette and erythema scores = 0), % (SE)	13.7 (2.4)	1.0 (0.7)
Difference in proportion cured (SE)[b]	0.1272 (0.0245)	
p-value[c]	< 0.0001	
p-value[d]	< 0.0001	

SE = standard error
The secondary efficacy endpoint of eradication of *Demodex* mites was based on the proportion of subjects with a mite density of 0 at Day 43. The secondary efficacy endpoint of composite cure was based on the proportion of subjects achieving both collarette and erythema scores of 0 at Day 43.
a Study drug withdrawal and/or nonoptimal compliance was ignored. Missing data were imputed as failures.
b The difference was computed as TP-03 minus vehicle.
c The p-value was from on a difference of proportions test.
d The p-value was based on Pearson's chi-squared test (or Fisher's exact test if any of the expected cell counts were < 5).
Source: Sponsor's study report, Table 16.

study 010

Table 5. 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 (Randomized Population)

	TP-03 N = 203	Vehicle N = 209
Cured (collarette score = 0), % (SE)	54.7 (3.5)	12.2 (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 TP-03 minus vehicle.
b The p-value was from a difference of proportions test.
Source: Sponsor's study report, Table 12.

Table 6. 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)

	TP-03 N = 203	Vehicle N = 209
Eradication of *Demodex* mites		
Cured (mite density = 0), % (SE)	49.9 (3.6)	14.0 (2.4)
Difference in proportion cured (SE)[a]	0.3588 (0.0432)	
p-value[b]	< 0.0001	
Composite cure		
Cured (collarette and erythema scores = 0), % (SE)	18.7 (2.8)	3.9 (1.4)
Difference in proportion cured (SE)[a]	0.1482 (0.0309)	
p-value[b]	< 0.0001	
Erythema cure		
Cured (erythema score = 0), % (SE)	30.3 (3.3)	9.1 (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 TP-03 minus vehicle.
b The p-value was from a difference of proportions test.
Source: Sponsor's study report, Table 15.

Table 7. Study TRS-010: Sensitivity Analyses of the Primary Endpoint (Full Analysis Set or Per Protocol Analysis Set, as Specified)

	TP-03 N = 203	Vehicle N = 209
Sensitivity analysis I (FAS with imputations for missing data)[a]		
Cured (collarette score = 0), % (SE)	53.8 (3.5)	12.2 (2.3)
Difference in proportion cured (SE)	0.4164 (0.0422)	
p-value[b]	< 0.0001	
Sensitivity analysis II (FAS with imputations for missing data)[c]		
Cured (collarette score = 0), % (SE)	55.3 (3.6)	12.2 (2.3)
Difference in proportion cured (SE)	0.4307 (0.0423)	
p-value[b]	< 0.0001	
Sensitivity analysis III (PP analysis set with observed data)[d]		
Cured (collarette score = 0), n/N (% [SE])	107/197 (56.3 [3.6])	25/202 (12.9 [2.4])
Difference in proportion cured (SE)	0.4343 (0.0433)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	
Sensitivity analysis IV (FAS with observed data)[f]		
Cured (collarette score = 0), n/N (% [SE])	108/203 (56.0 [3.6])	25/209 (12.5 [2.3])
Difference in proportion cured (SE)	0.4346 (0.0427)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	
Sensitivity analysis V (FAS with imputations for missing data)[g]		
Cured (collarette score = 0), n/N (% [SE])	108/203 (53.2 [3.5])	25/209 (12.0 [2.2])
Difference in proportion cured (SE)	0.4124 (0.0416)	
p-value[b]	< 0.0001	
p-value[e]	< 0.0001	

FAS = full analysis set; PP = per protocol analysis set; SE = standard error

The primary efficacy endpoint was the proportion of subjects achieving a cure (collarette score = 0) in the upper eyelid of the analysis eye at Day 43.

Differences between study drug groups were calculated as TP-03 minus vehicle.

a Missing data were imputed assuming they were not missing at random (ie, imputing from the vehicle group), with the analysis based on the FAS. Multiple imputation datasets were used to calculate cure based on a collarette score of 0 at Day 43.

b The p-value was from a difference of proportions test.

c Missing data were imputed assuming they were missing at random (ie, imputing from the same study drug group as the subject with the missing data), with the analysis based on the FAS. The multiple imputation datasets were used to calculate cure based on a collarette score of 0 at Day 43.

d Using observed data at Day 43 in the per protocol analysis set, N = 199 for the TP-03 group and N = 204 for the vehicle group.

e The p-value was based on Fisher's exact test.

f Using observed data at Day 43 in the FAS, N = 203 for the TP-03 group and N = 209 for the vehicle group.

g All missing data were imputed as failures.

Source: Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4, Table 14.2.2.5, and Table 14.2.2.6

Table 8. Study TRS-010: Sensitivity Analyses of the Secondary Efficacy Endpoints (Full Analysis Set)

	TP-03 N = 203	Vehicle N = 209
Eradication of *Demodex* mites[a]		
Cured (mite density = 0), n/N (% [SE])	100/203 (49.3 [3.5])	29/209 (13.9 [2.4])
Difference in proportion cured (SE)[b]	0.3539 (0.0425)	
p-value[c]	< 0.0001	
p-value[d]	< 0.0001	
Composite cure[a]		
Cured (collarette and erythema scores = 0), n/N (% [SE])	37/203 (18.2 [2.7])	8/209 (3.8 [1.3])
Difference in proportion cured (SE)[b]	0.1440 (0.0302)	
p-value[c]	< 0.0001	
p-value[d]	< 0.0001	
Erythema cure[a]		
Cured (erythema scores = 0), n/N (% [SE])	60/203 (29.6 [3.2])	18/209 (8.6 [1.9])
Difference in proportion cured (SE)[b]	0.2094 (0.0374)	
p-value[c]	< 0.0001	
p-value[d]	< 0.0001	

SE = standard error
The secondary efficacy endpoint of eradication of *Demodex* mites was based on the proportion of subjects with a mite density of 0 at Day 43. The secondary efficacy endpoint of composite cure was based on the proportion of subjects achieving both collarette and erythema scores of 0 at Day 43.
a Study drug withdrawal and/or nonoptimal compliance was ignored. Missing data were imputed as failures.
b The difference was computed as TP-03 minus vehicle.
c The p-value was from on a difference of proportions test.
d The p-value was based on Fisher's exact test.
Source: Sponsor's study report, Table 16.

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