CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217603Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 20, 2023

To: Dheera Semidey, Regulatory Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for XDEMVY™ (lotilaner ophthalmic solution) 0.25%, for topical ophthalmic use

NDA: 217603

Background:
In response to DROSM's consult request dated October 27, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for XDEMVY™ (lotilaner ophthalmic solution) 0.25%, for topical ophthalmic use.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on June 18, 2023, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on June 5, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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Clinical Inspection Summary

Date	April 28, 2023
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D, Deputy Division Director Rhea Lloyd, M.D., Clinical Team Leader Martin Nevitt, M.D., Reviewing M.O. Ahmed Ayodeji, P.M. Division of Ophthalmology
NDA	217603
Applicant	Tarsus Pharmaceuticals
Drug	Xdemvy (Lotilaner Ophthalmic Solution, 0.25%)
NME	No
Therapeutic Classification	Antiparasitic
Proposed Indication(s)	Treatment of *Demodex* blepharitis.
Consultation Request Date	4 Oct 22
Summary Goal Date	12 May 2023
Action Goal Date	23 Jun 2023
PDUFA Date	23 Jun 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols TRS-009 and TRS-010 were submitted to the Agency in support of NDA 217603 for the use of Xdemvy for the treatment of *Demodex* blepharitis. The clinical sites of Drs. Meyer, Paauw, Vollmer, and Schechter were inspected in support of this NDA.

At Dr. Schecter's site, four subjects, although not eligible for the study, were enrolled, randomized, and dosed. This protocol deviation was reported to the FDA. Otherwise, Studies TRS-009 and TRS-010 appear to have been conducted adequately and the data generated by the inspected sites appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Xdemvy, an antiparasitic agent, for the treatment of *Demodex* blepharitis.

Inspections were requested of the following protocols in support of this application:

Protocol Number: TRS-009

Title: 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)

TRS-009 was a Phase 2b/3 study that was a randomized, controlled, multicenter, double-masked, parallel trial whose objective was to compare the safety and efficacy of TP-03 (lotilaner) to vehicle control for the treatment of Demodex blepharitis.

Qualifying subjects were randomized 1:1 to either active study medication or vehicle control with subjects administering one drop of the investigational product to each eye twice daily (mornings and evenings). Efficacy assessments included assessment of collarette grade, eyelash epilation and mite counts, and assessment of erythema grade. Safety measurements included corrected distance visual acuity, adverse events, intraocular pressure (IOP) measurements, slit lamp biomicroscopy assessment, dilated fundus examination, and drop comfort. The primary efficacy endpoint was the proportion of participants cured based on their collarette score of the upper eyelid of the analysis eye at Day 43.

Study TSP-009 was conducted at 15 study centers in the U.S. The study period was from 09 September 2020 (first subject, first visit) to 04 May 2021. A total of 421 subjects were randomized to the study.

Protocol Number: TRS-010

Title: 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)

Study TRS-010 was very similar to Protocol TRS-009 in terms of design, objective, and primary efficacy endpoint. The duration of the study is somewhat longer as there was a Day 57 Visit (for Cohort 1) and a Day 90 Visit (for sites performing specular microscopy). As with TRS-009, the primary efficacy endpoint was defined as the cure based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43.

Study TSP-010 was conducted at 21 study centers in the U.S. The study period was from 29 April 2021 (first subject, first visit) to 21 March 20222 (last subject, last visit for Milestone 1). A total of 412 subjects were randomized to the study.

III. RESULTS:

1. John C Meyer, MD
The Eye Care Institute
1536 Story Avenue
Louisville, KY 40206

Protocol: TRS-009
Site: 05
Inspection Dates: 8-14 Feb 2023

Dr. Meyer was inspected for the conduct of Protocol TRS-009. At this site, 104 subjects were screened, 60 were enrolled, and one subject withdrew as the result of a serious adverse event (pneumonia).

The primary efficacy endpoint and adverse event reporting data were verified against the data listings. Other subject records reviewed included inclusion/exclusion criteria, informed consent, medical histories, randomization concomitant medications, protocol deviations, paper and electronic case report forms (CRFs), and subject diaries. Study related documents reviewed included IRB submissions and approvals, site correspondence, monitoring reports, investigational product (IP) accountability logs, training logs, Form 1572s, delegation logs, and financial disclosure documents.

The inspection compared the source records with the eCRFs and the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate. No Form FDA 483 was issued to Dr. Meyer.

2. James Paauw, MD
Piedmont Eye Center
116 Nationwide Drive
Lynchburg, VA 24502

Protocol: TRS-009
Site: 06
Inspection Dates: 17-19 Jan 2023

Dr. Paauw was inspected for the conduct of Protocol TRS-009. At this site, 132 subjects were screened, 71 were enrolled, along with 61 screen failures, three discontinuations, and one subject lost to follow up.

The primary efficacy endpoints were verified for 24 of the enrolled subjects. There was no evidence of under-reporting of adverse events. Other subject records reviewed for these 24 subjects included study eligibility, informed consent, medical histories, study randomization, IP administration, protocol deviations, concomitant medications, protocol deviations, paper

and electronic CRFs, and subject diaries. Study related documents reviewed included IRB submissions and approvals, site correspondence, monitoring reports, IP accountability logs, training logs, Form 1572s, delegation logs, and financial disclosure documents.

The inspection compared the source records with the eCRFs and the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate. No Form FDA 483 was issued to Dr. Paauw

3. Patrick Vollmer, OD
Vita Eye Clinic
222 N Lafayette St, Suite 12
Shelby, NC 28150

Protocol: TRS-010
Site: 08
Inspection Dates: 15-20 Dec 2023

Dr. Vollmer was inspected for the conduct of Protocol TRS-010. At this site, 114 subjects were screened, 79 were enrolled, 35 failed screening, and three subjects withdrew consent. The primary efficacy endpoint, adverse events, and randomization source documents were verified against the FDA line listings and no discrepancies were observed. There was no evidence of under-reporting of adverse events. Other subject records reviewed included medical histories, inclusion/exclusion criteria, informed consent, visual acuity testing, concomitant medications, protocol deviations, laboratory tests, paper worksheets, eCRFs including password access and accompanying audit trails, and questionnaires. Study related documents reviewed included financial disclosure reports, delegation logs, IRB submissions and approvals, site correspondence, monitoring reports, and IP accountability,

The inspection compared the source records and eCRFs with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate. No Form FDA 483 was issued to Dr. Vollmer.

4. Scott Schecter, OD
Pinnacle Research Institute
2900 West Cypress Creek Road, Suite 10
Fort Lauderdale, FL 33309

Protocol: TRS-010
Site: 22
Inspection Dates: 30 Jan-6 Feb 2023

Dr. Schecter was inspected for the conduct of Protocol TRS-010. At this site, 78 subjects were screened, 56 were enrolled, 15 failed screening, five discontinued the study, one withdrew consent, and one subject was lost to follow up. The primary efficacy endpoint data were verified against the FDA line listings and no significant discrepancies were noted.

Review of the subject source records indicated that adverse events were reported appropriately and there was no evidence of under-reporting of adverse events. Other subject records reviewed included informed consent forms, medical histories, inclusion/exclusion criteria, concomitant medications, laboratory reports, protocol deviations, and study progress notes. Study related documents reviewed included financial disclosure reports, delegation logs, IRB submissions and approvals, site correspondence, monitoring reports, and IP accountability.

A Form FDA 483 was issued to Schecter because review of the inclusion/exclusion criteria revealed that four subjects were screened, randomized, and dosed despite not meeting inclusion criteria or meeting exclusion criteria. The subjects included:

- Subject (b) (6) was screened, randomized, and dosed on (b) (6) despite taking Symbicort until (b) (6). Use of this medication was exclusionary within 14 days of screening.
- Subject (b) (6) was screened, randomized, and dosed on (b) (6) but did not meet the inclusion criteria of 10 lashes with collarettes score of 2 or greater and Demodex density upper and lower eyelids combined of 1.5 or more mites per lash in the same study eye.
- Subject (b) (6) was screened, enrolled, and randomized/dosed on (b) (6) while taking a topical ocular prostaglandin concomitant medication starting on (b) (6). Protocol inclusion criteria required that the subject be on a stable dose for 30 days or more prior to screening.
- Subject (b) (6) was screened, enrolled, and randomized/dosed on (b) (6) while taking erythromycin beginning on (b) (6). The use of erythromycin was exclusionary if taken within 14 days of the screening visit.

Reviewer's Note: Dr. Schecter's written response acknowledged the above protocol deviations and implemented corrective actions including a secondary review by quality assurance staff of medical histories and concomitant medications along with relevant start and stop dates. Dr. Schecter's response and corrective actions appear adequate. The protocol deviations appear isolated and were reported in the data listings of the application.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
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Jenn Sellers, M.D., Ph.D.
Branch Chief
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CC:
Central Doc. Rm.
DO/Division Director/Wiley Chambers
DO/Deputy Director/William Boyd
DO/Medical Team Leader/Rhea Lloyd
DO/Medical Officer/Martin Nevitt
DO/Project Manager/Ahmed Ayodeji
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 17, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217603
Product Name and Strength:	Xdemvy (lotilaner ophthalmic solution), 0.25%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Tarsus Pharmaceuticals, Inc.
FDA Received Date:	August 25, 2022
TTT ID #:	2022-1050
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 REASON FOR REVIEW

As part of the approval process for Xdemvy (lotilaner ophthalmic solution), the Division of Ophthalmology (DO) requested that we review the proposed Xdemvy prescribing information (PI), physician sample and trade container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (For Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), professional sample and trade container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Tarsus Pharmaceuticals, Inc..

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, we note the statement on handling missed	201.57(c)(3)(i)(I), states that Section *2 Dosage and Administration* of the full	Include the instruction on handling *Missed Dose* to

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	doses *"Advise patients that if one dose is missed, treatment should continue with the next dose"* included in *Section 17 Patient Counseling Information* under the subheading "*Missed Dose.*" However, this important dosing information is not included under the *"Section 2 Dosage and Administration"* of the PI.	prescribing information "must state the recommended dose and, as appropriate important considerations concerning compliance with dosage regimen"	*Section 2 Dosage and Administration* of the FPI.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented the appropriate information to facilitate identification of the dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57 (c)(17)(iii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57 (c)(17)(iii).

5 RECOMMENDATIONS FOR TARSUS PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Tarsus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Professional Sample and Trade Container Labels and Carton Labeling			
1.	As currently presented, we note the product strength is included within the parenthesis with the established name (i.e., "Xdemvy (lotilaner ophthalmic solution 0.25%)").	The strength statement is not part of the established name and should be presented outside the parenthesis.	We recommend revising such that the strength appears outside of the parenthesis as: "Xdemvy (lotilaner ophthalmic solution) 0.25%"

Table 3. Identified Issues and Recommendations for Tarsus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	As currently present the format for expiration date is stated as "MM YYYY." As stated, it is not clear how the month will be abbreviated.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. For example, presenting the month as 'MA' or 'JU' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and June or July, respectively.	Clarify how you intend to express the month abbreviation within the expiration date statement. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
3.	As currently presented, a space is not provided for users to write in the date of fist opening of the bottle.	Lack of an allotted space to write in the date of first opening of the bottle may lead to use beyond 42 days.	We recommend including the statement "Date of first opening __/__/__." Additionally, on the carton labeling this statement can be included following the statement "Instill one drop of XDEMVY in each eye twice daily for 42 days."

Table 3. Identified Issues and Recommendations for Tarsus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Professional Sample and Trade Carton Labeling			
1.	The expiration date format is not included.	Including a clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Include and define the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
Professional Sample and Trade Carton Labeling – General			
2.	Consider revising the usual dosage statement to include a heading to better identify it as the usual dosage statement, for example, consider revising to: "Dosage: Instill one drop of Xdemvy in each eye twice daily for 42 days."		
Professional Sample and Trade Container Labels			
3.	As currently presented, the linear barcode is in a	Barcodes placed in a horizontal position may not	We recommend, reorienting the linear barcode to a vertical

Table 3. Identified Issues and Recommendations for Tarsus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	horizontal position the professional sample and trade container labels.	scan due to container curvature.	position to improve scannability of the barcode.
4.	As currently presented, the units of temperature measure (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges on the professional sample and trade container labels.	The lower temperature in the ranges may be overlooked.	We recommend revising the storage statement to include Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example: "15°C to 25°C (59°F to 77°F)
5.	Some statements on the trade container label overlap on top of each other. For example: (b) (4)	A clearly formatted container label will minimize the risk of confusion that could lead to medication errors.	Ensure the trade container label is clearly formatted to increase readability of each statement presented.
Trade Carton Labeling			
1.	As currently presented, we note that the product identifier is not included on the carton labeling.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifier recommends a machine-	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act* –

Table 3. Identified Issues and Recommendations for Tarsus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the human-readable product identifier to the container label. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	*Questions and Answers* (July 2021).[a] If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder to the carton labeling. Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.
Professional Sample Container Label			
1.	The container label does not include a statement clearly denoting its status as a drug sample.	The container label and carton labeling should clearly denote the packaging configuration as professional sample in accordance with 21 CFR203.38(c).	Include a statement to denote the product as a drug sample on the container label as required by 21 CFR 203.38(c). You may choose to use the statement "Physician Sample" in alignment with the carton labeling.

[a] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xdemvy that Tarsus Pharmaceuticals, Inc. submitted on August 25, 2022.

Table 4. Relevant Product Information for Xdemvy	
Initial Approval Date	N/A
Active Ingredient	Lotilaner
Indication	The treatment of Demodex blepharitis
Route of Administration	Topical ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.25%
Dose and Frequency	Instill one drop of XDEMVY in each eye twice daily (approximately 12 hours apart) for 6 weeks.
How Supplied	10 mL fill in a 11 mL container NDC 81942-125-01
Storage	15°C to 25°C (59°F to 77°F). (b) (4) . After opening the XDEMVY bottle, it can be used (b) (4) .
Container Closure	Sterile ophthalmic solution in a low-density polyethylene (LDPE) (b) (4) bottle (11 mL) with a LDPE dropper tip and high-density polyethylene (HDPE) cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 1, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, lotilaner and 217603. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Xdemvy labels and labeling submitted by Tarsus Pharmaceuticals, Inc..

- Trade Container label received on August 25, 2022
- Trade Carton labeling received on August 25, 2022
- Professional Sample container label received on August 25, 2022
- Professional Sample Carton labeling received on August 25, 2022
- Prescribing Information (Image not shown) received on August 25, 2022, available from
    - Annotate version: \\CDSESUB1\EVSPROD\nda217603\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf
    - Clean version: \\CDSESUB1\EVSPROD\nda217603\0001\m1\us\114-labeling\draft\labeling\proposed-labeling-text-pdf.pdf

F.2 Label and Labeling Images

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217603
Submission Number	001
Submission Date	8/25/2022
Date Consult Received	9/13/2022
Drug Name	TP-03 (lotilaner) ophthalmic solution, 0.25%
Indication	Treatment of Demodex blepharitis
Therapeutic Dose	Administration of 0.25 % lotilaner twice daily by the topicalophthalmic route
Clinical Division	DO
Protocol Review	No previous protocol review

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 9/13/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-143686 dated 02/28/2022 (link) and dated 03/30/2022 (link) in DARRTS;
- Sponsor's protocol #TRS-013 (SN0009; link);
- Sponsor's cardiac safety analysis report (SN0001; link);
- Sponsor's modeling and simulation analysis plan (SN0001; link);
- Sponsor's proposed labeling (SN0001; link);
- Sponsor's partial response dated 09/16/22 (SN0002; link);
- Sponsor's summary clinical study report of safety for #TRS-013 (SN0003; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; link).

1 SUMMARY

No significant QTcF prolongation effect of lotilaner was detected in this QTc assessment of data collected in Study TRS-013. This study can be used as a substitute for a TQT study under E14 Q&A 5.1.

The effect of lotilaner was evaluated in an approach of extending concentration-QT assessment characterized using oral product to ophthalmic product. Study TRS-013 was a randomized, double-blind study in healthy subjects. The highest dose that was evaluated was 600 mg (as a single dose), which covers the overdose exposure scenario (patients orally ingest a 30 mL bottle (75 mg); Section 3.1). Assay sensitivity was established using exposure margin (8-fold of the overdose exposure scenario). Data were analyzed

using exposure-response analysis as the primary analysis, which did not suggest that lotilaner is associated with significant QTc prolonging effect (refer to Section 4.5) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results.

Table 1. Mean (90% CI) predicted ΔΔQTcF (FDA Analysis)

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The highest dose tested in clinical QT study is 600 mg single dose, which provides >200 times coverage of the highest therapeutic topical dose.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTc</td><td>Lotilaner 100 mg single dose by oral adminstration</td><td>678.5 ng/mL</td><td>3.1</td><td>(-0.9 to 7.2)</td></tr>
<tr><td>QTc</td><td>Lotilaner 600 mg single dose by oral adminstration</td><td>4,522.6 ng/mL</td><td>-0.8</td><td>(-6.4 to 4.8)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">An integrated nonclinical risk assessment was not performed because the clinical study included a large exposure margin to waive positive control.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The sponsor did not propose QT labelling for lotilaner. Below is the proposed label language from the CSS-IRT. Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division

12.2 Pharmacodynamics Cardiac Electrophysiology At exposures >200-times the exposures at the maximum approved recommended topical dose, lotilaner does not prolong the QTc interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Tarsus Pharmaceuticals, Inc. is developing lotilaner for the treatment of blepharitis (due to Demodex infestation). Lotilaner (TP-03; MW: 596.76 g/mol, isooxazoline derivative) is inhibitors of γ–aminobutyric acid-gated chloride channels (GABACls) which generate inhibitory postsynaptic potentials in the neurons of Demodex mites and are important to normal mite nervous system function. Refer to previous IRT review dated 03/30/2022 in DARRTS.

(b) (4)

. Mean peak concentrations of 17.8 ng/mL (Tmax: ~1 h) were obtained at steady state with the proposed therapeutic dosing regimen of twice daily topical ocular administration of lotilaner 0.25% solution. In addition, the risk of QT prolongation associated with ocular administration of lotilaner has not been adequately characterized in Study TRS-012 (an open-label, single arm study) routine safety ECGs were collected at screening, on day 42 (4 hours after dosing) and at the end of study visit.

Then the Sponsor proposed extending concentration-QT assessment characterized using oral product to ophthalmic product, which appeared adequate to characterize the QTc prolongation potential of ophthalmic product and can potentially serve as an alternative to the TQT study (ICH E14 Q&A (R3) 5.1). Study # TRS-013 was a randomized, double-blind, placebo-controlled, parallel-group, single (25 mg, 100 mg, 400 mg and 600 mg, & 600 mg for FE; n=40) and multiple (n=30) ascending dose study evaluating safety, tolerability, food effect, and pharmacokinetics of lotilaner. SAD part of the study included matched PK/ECGs. The mean peak concentration (Cmax: ~4990 ng/mL) observed with highest dose studied (i.e., 600 mg single oral dose) is expected to offer ~280- fold margin over the therapeutic exposures (Steady state mean Cmax: ~17.8 ng/mL) associated with the maximum proposed dose for ophthalmic product (i.e., TP-03, 0.25%) at the steady-state. Additionally, the worse case scenario would be if someone orally ingested the topical ophthalmic formulation. If 0.5 mg is administered daily by the ophthalmic route then orally ingesting a 30 mL bottle would be ingesting 75 mg. The

peak concentration with highest dose studied (i.e., 600 mg single oral dose) in Study TRS-013 is expected to offer ~280- fold margin over the therapeutic exposures and therefore a positive control is not necessary.

No significant QTcF prolongation effect of lotilaner was detected in this QT assessment.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety (link).

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	0.25 % Lotilaner will be administered BID by the topical ophthalmic route for 42 days.	17.8 ng/mL ($C_{max,ss}$)
Sponsor's High clinical exposure scenario	High clinical exposure scenario is not yet known. But worst-case exposure can occur when a patients overdose by orally ingesting a 30 mL bottle (75 mg)	678.5 ng/mL (after 100 mg single dose)
Highest dose in QT assessment	600 mg oral tablets	4990 ng/mL
C_{max} Ratio over therapeutic Cmax	280	

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for Lotilaner was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *The statistical reviewer evaluated the ΔΔQTcF effect using descriptive nonparametric statistics. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. Please see Section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are the same with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper to explore the relationship between plasma concentration of lotilaner and ΔΔQTcF (placebo-corrected change from baseline in QTcF). The sponsor analysis indicates a slight negative slope of -0.000715 msec/μg/mL (90% CI: -0.00172, 0.000289 msec/μg/mL) between lotilaner concentration and ΔΔQTcF.

The model predicted ΔΔQTcF (upper 90% confidence interval) values of 3.07 (6.8) msec at the mean peak concentrations at 100 mg (geomean Cmax 678.5 ng/mL) following single dose which is close to high clinical exposure scenario. Similarly, the model predicted ΔΔQTcF (upper 90% confidence interval) values of 0.316 (5.22) msec at the mean peak concentrations for 600 mg (geomean Cmax 4522.6 ng/mL) following single dose.

The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic dose (i.e., TP-03, 0.25 % Lotilaner will be administered BID by the topical ophthalmic route).

Reviewer's comment: *The sponsor's results are similar to the reviewer's results.*

3.2.4 Cardiac Safety Analysis

There were no deaths. One subject in the MAD placebo group experienced a nonfatal SAE (gun shot wound) and 1 subject in TP-05 Cohort 6 discontinued the study due to a TEAE (COVID-19); both events were considered by the investigator to be unrelated to study drug. There were no cardiac-related TEAEs.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.)*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable

4.3 BY-TIME ANALYSIS

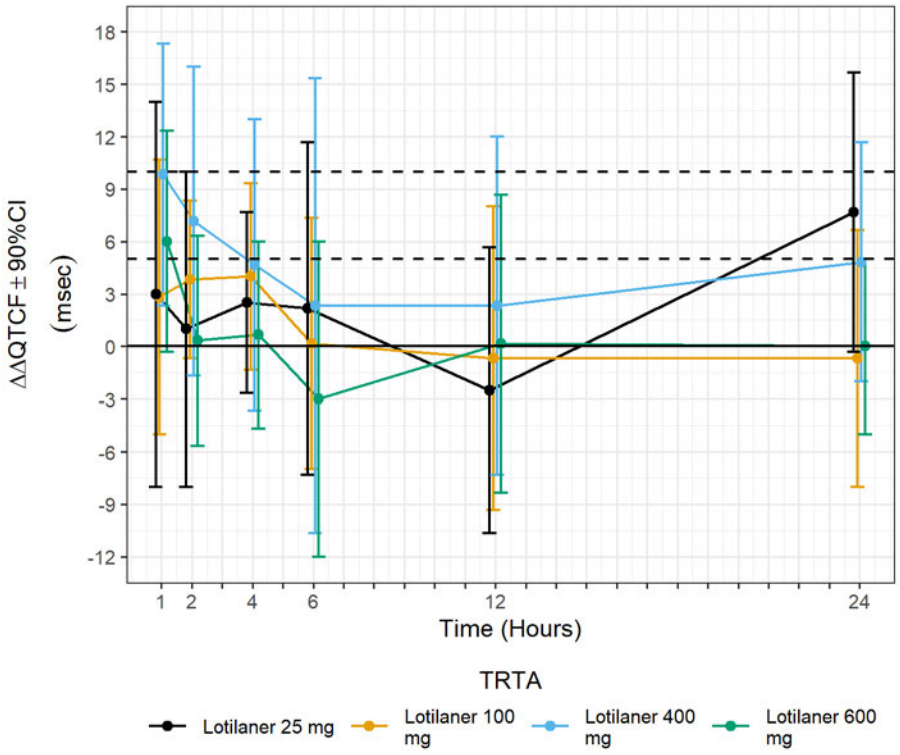
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).



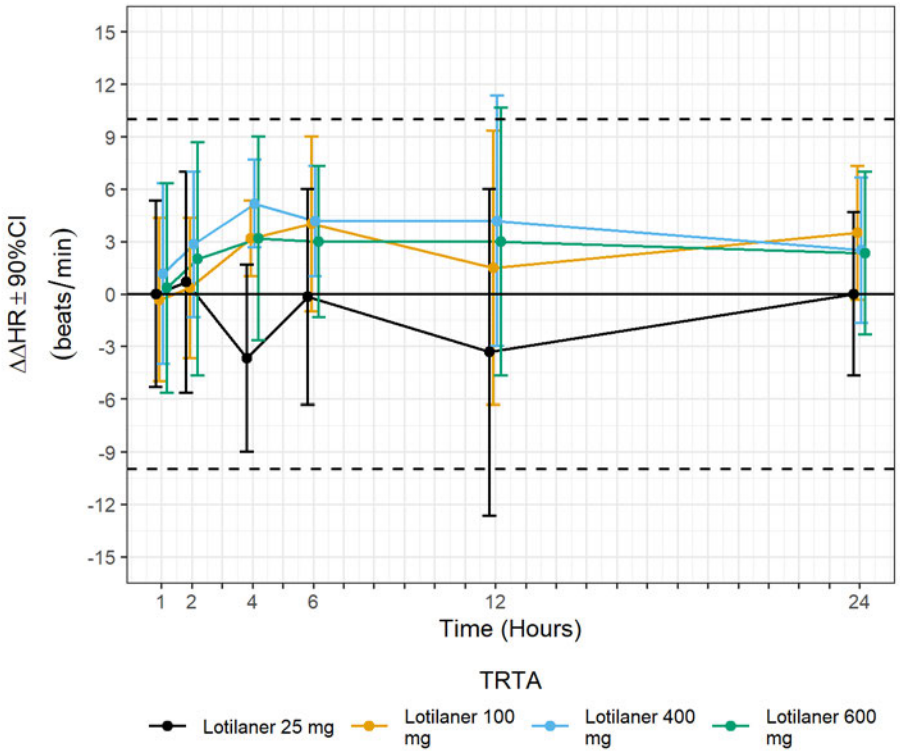
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

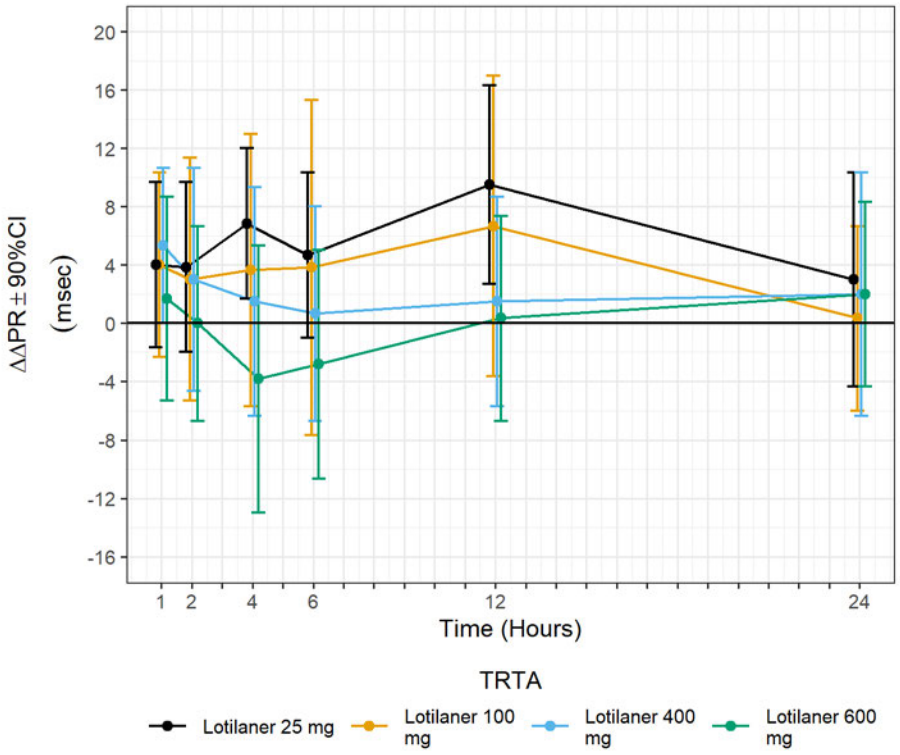
Figure 2: Median and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

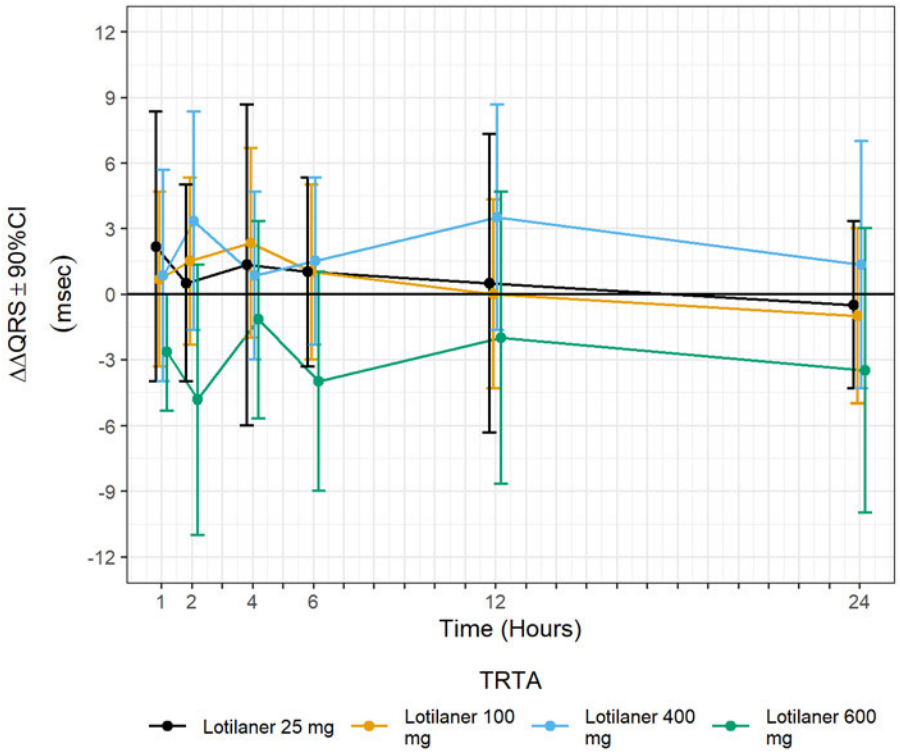
Figure 3: Median and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec or change from baseline above 30 msec.

4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

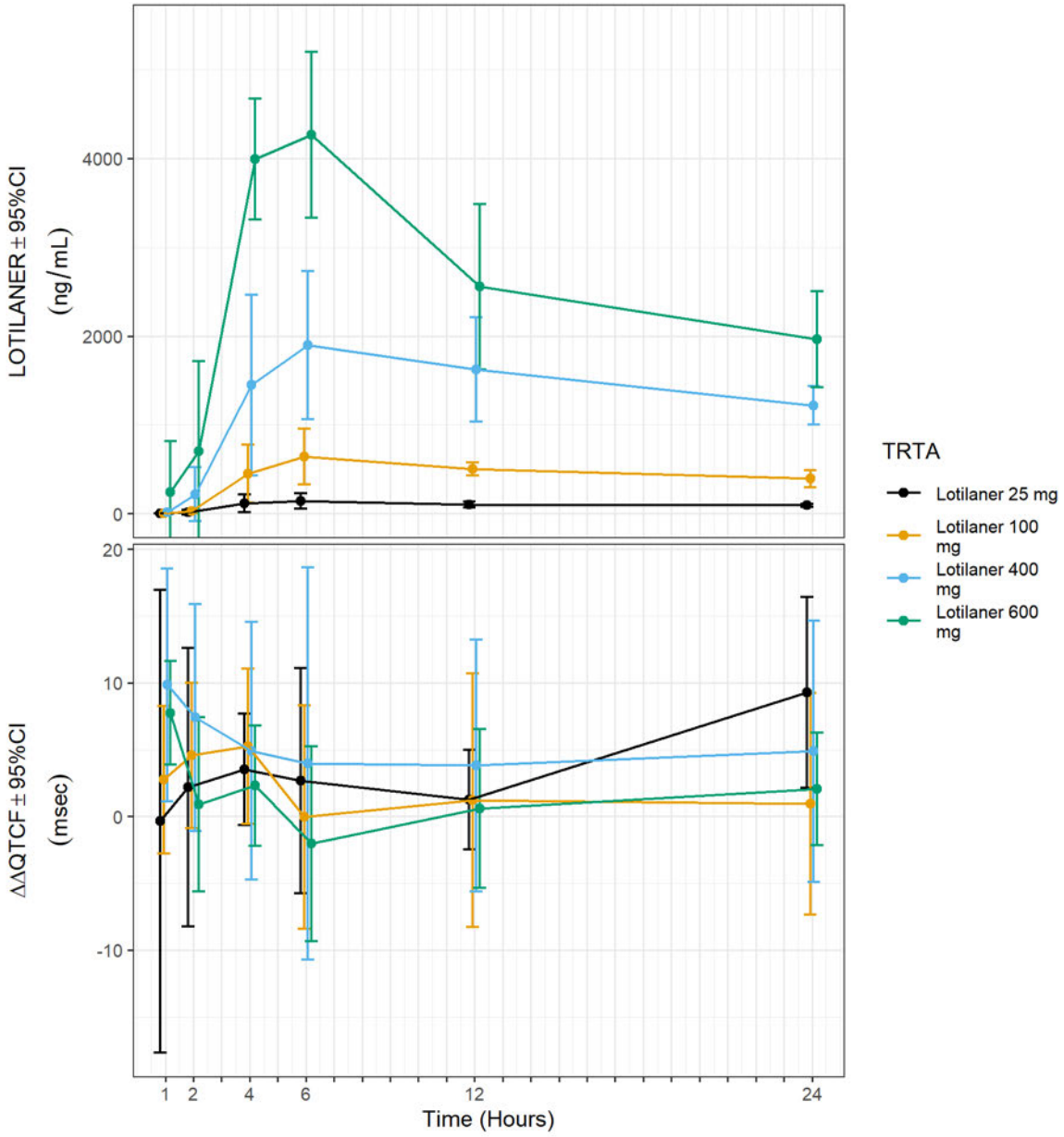
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. An evaluation of the relationship between time-course of lotilaner concentration and ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of lotilaner indicating no significant hysteresis.

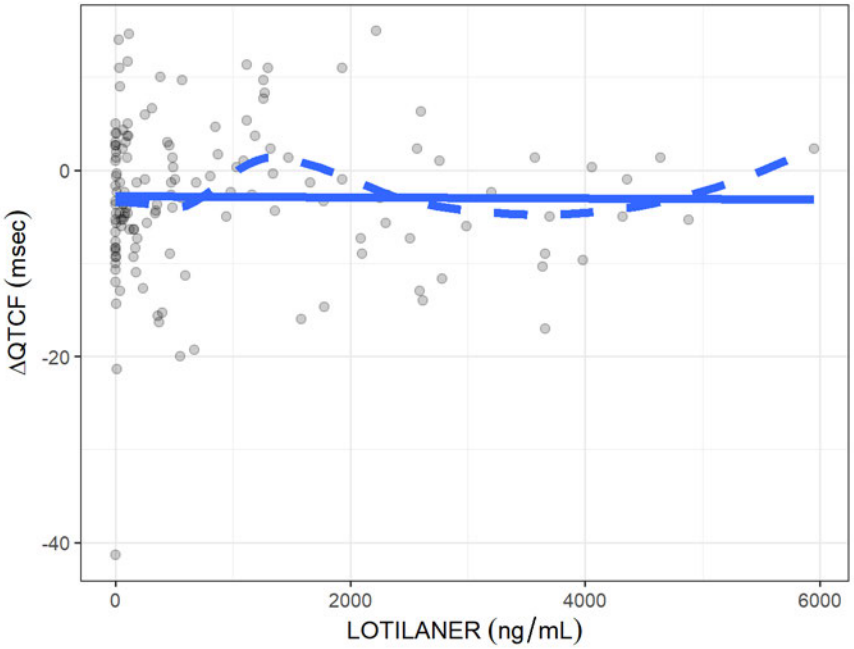
Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between lotilaner concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between lotilaner concentration and ΔΔQTc and supports the use of a linear model.

[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 3.

Figure 7: Goodness-of-fit Plot for QTcF

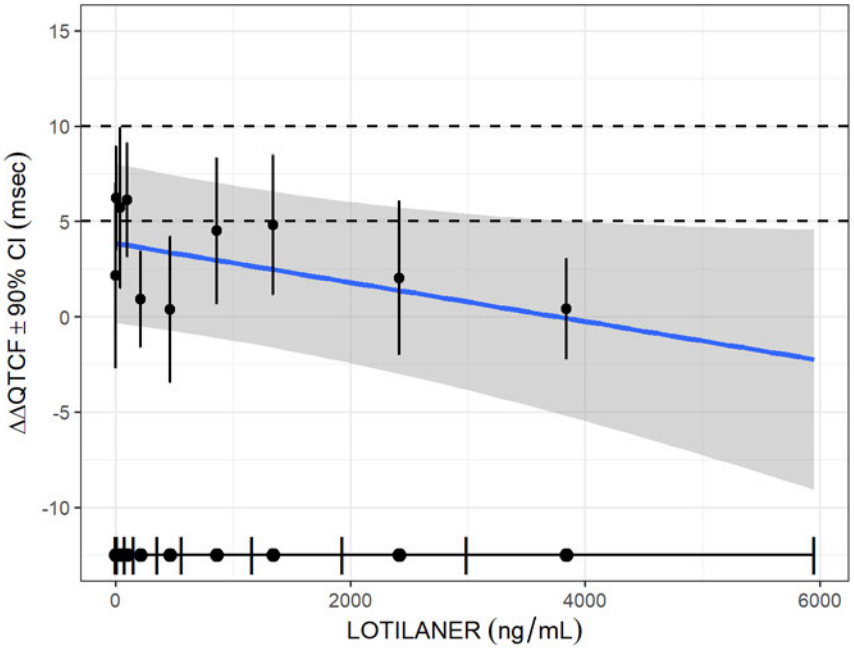


Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	LOTILANER (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Lotilaner 25 mg	1	168.5	3.7	(-0.5 to 7.8)
Lotilaner 100 mg	1	678.5	3.1	(-0.9 to 7.2)
Lotilaner 400 mg	1	2,155.3	1.6	(-2.6 to 5.9)
Lotilaner 600 mg	1	4,522.6	-0.8	(-6.4 to 4.8)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Lotilaner	Brand Name	XDEMVY
Drug Class	A gamma-aminobutyric acid (GABA)-gated chloride channel inhibitor		
Combination Product	No		
Indication	Treatment of Demodex blepharitis		
Therapeutic Dose	Administration of 0.25 % lotilaner twice daily by the topicalophthalmic route		
Maximum Tolerated Dose	600 mg orally		
Dosage Form	Ophthalmic solution	Route of Administration	Ocular administration

2. QT Studies								
2.1 Primary Studies								
Protocol Number / Population	**ECG Quality**		**Arms**		**Sample Size**		**ECG & PK Assessments**	
	Assessment	**OK?**	**Arms**	**High Dose Covers?**	**No Subjects**	**OK?**	**Timing**	**OK?**
Protocol Number: TRS-013 Population: Healthy volunteers	Central Read? Unknown Blinded? Yes Replicates? Yes	Yes	Highest Dose: 600 mg orally Placebo: Yes	(b) (4)	A total of 32 subjects. 8 subjects received Lotilaner or placebo (6 active: 2	Yes	Baseline: Pre-dose baseline Timing: Screening and Day -1, and triplicate 12-lead ECGs on Day 1, predose, 1, 2, 4, 6,	*Yes*

Design: Parallel			Positive Control: No		placebo) per cohort.		12, and 24 hours postdose, and prior to discharge on Day 3. A final set of triplicate 12-lead ECGs will be collected at the last follow up visit (Day 121).	

2.2 Secondary Studies	
None.	
2.3 Data Pooling	
Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	No
Is the data pooling appropriate?	N/A
N/A	
3. Analysis plan	
3.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	10 ms (E14)
N/A.	
3.2 Dose Justification	
The worst-case scenario is if someone orally ingested the topical ophthalmic formulation (30 mL with 75 mg lotilaner). In Study Study TRS-013, the highest dose tested was 600 mg single dose, which provides 8-fold coverage of the worst-case exposure scenario.	
3.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No

Primary method for QT correction	QTcF
N/A.	
3.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☒ Exposure-margin ☐ QT bias assessment ☐ Other ☐ Not applicable (objective is large mean effects)
N/A.	
3.5 By-Time Analysis	
3.5.1 Investigational Drug	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the sponsor use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	N/A
N/A.	
3.5.2 Positive Control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	N/A
N/A.	
3.6 Exposure-Response Analysis	
3.6.1 Investigational Drug	

Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Parent
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes
Which methods did the sponsor use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
N/A	
3.6.2 Positive Control	
Primary analysis	No
Same model as investigational drug	N/A
N/A	

3.7 Categorical Analysis			
QTcF?	Yes	QRS?	Yes
ΔQTcF?	Yes	HR?	Yes
PR?	Yes	T-wave morphology?	No

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/s/

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