STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title:	Randomized, Double-Masked, Pilot Study Comparing the Safety and Efficacy of Two Dosing Regimens of TP-03 for the Treatment of Meibomian Gland Dysfunction in Patients with Demodex Lid Infestation (Ersa)
Protocol Number:	TRS-008
Protocol Version (Date):	Version 4.0 (01Feb2023)
Clinicaltrials.gov Identifier	NCT05454956
Sponsor:	Tarsus Pharmaceuticals, Inc.
SAP Version (Approved Date)	Revision A (13Apr2023)

Tarsus Pharmaceuticals, Inc.
Protocol #: TRS-008

Protocol Name:

Randomized, Double-Masked, Pilot Study Comparing the Safety and Efficacy of Two Dosing Regimens of TP-03 for the Treatment of Meibomian Gland Dysfunction in Patients with Demodex Lid Infestation (Ersa)

[redacted]

Protocol Version: 4.0 Amendment 3, dated 01February2023

NCT05454956

Statistical Analysis Plan

[redacted]

SAP Approval

By signing the following, I agree to the contents in the Statistical Analysis Plan and its associated attachments. Once the SAP has been signed, the analyses and programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a change order.

Approved by:

Name	Title	Signature	Date
[redacted]	[redacted]	[redacted] Signer Name: [redacted]	4/13/2023
[redacted]	Principal Consultant, CTDS	[redacted] [redacted] Signing Reason: I approve this document Signing Time: 3/31/2023 | 4:06:21 PM PDT ED90A6839EA8427392270CC83D722157	

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BLISS	BLepharItiS Symptom measure
CDVA	Corrected Distance Visual Acuity
CI	Confidence interval
CTDS	Clinical Trial Data Services
ETDRS	Early Treatment Diabetic Retinopathy Study
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian gland dysfunction
MGSS	Total meibomian gland secretion score
NEI	National Eye Institute
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
[redacted]	[redacted]
TEAE	Treatment emergent adverse event
TRS	Tarsus
VA	Visual acuity
VAS	Visual analog scale

TABLE OF CONTENTS

[redacted]

1 Protocol Summary

Title	Randomized, Double-Masked, Pilot Study Comparing the Safety and Efficacy of Two Dosing Regimens of TP-03 for the Treatment of Meibomian Gland Dysfunction in Patients with *Demodex* Lid Infestation (Ersa)
Test Article	TP-03, lotilaner ophthalmic solution, 0.25%
Other Test Article	Vehicle of TP-03 to maintain masking of BID dosing
Objective	To evaluate the safety and efficacy of TP-03, 0.25%, BID versus TID dosing for the treatment of meibomian gland dysfunction in patients with *Demodex* lid infestation. Efficacy will be evaluated by the assessment of lower lid meibomian gland secretion, erythema of the lid margins, [redacted] Safety will be determined by assessing adverse effects related to treatment [redacted]
Clinical Hypothesis	Treatment with TP-03, 0.25%, TID will result in a greater improvement from baseline than BID treatment for 85 days in the signs [redacted] of MGD with no significant increase in ocular irritation.
Study Design	Prospective, randomized, two-arm, double-masked, parallel treatment study
Number of Participants	Up to 40
Participant Population	Participants with evidence of meibomian gland dysfunction in the presence of *Demodex* infestation
Description of Sites	Up to six sites in the United States
Study Duration	Approximately 9 months
Randomization	1:1
Study Visits	Study visits will take place at Day 1 (Baseline), Day 15, Day 29, Day 43, Day 57 and Day 85
Safety Measures	• Adverse events • [redacted] • Slit lamp biomicroscopy findings

Efficacy Measures	• Lower lid meibomian gland secretion assessment
	  ○ Total meibomian gland score
	  [redacted]
	• Lid margin erythema
	[redacted]

Statistical Considerations	This is a pilot study to compare the safety and efficacy of two different dosing regimens, BID and TID, of TP-03 for the treatment of MGD. There are no prior data available to perform a sample size estimate. The sample size of 40 participants was selected based on clinical and practical considerations.
Statistical Analysis Plan	Safety measures will be summarized for each treatment regimen and both treatment regimens combined using descriptive statistics. Efficacy measures will be compared between dosing regimens as the change from baseline using either the t-test or Wilcoxon rank-sum test as appropriate. Comparisons will be two-sided using an α of 0.05. No adjustment will be made for multiple comparisons. Additional analyses will be performed examining the change from baseline in the efficacy measures for both treatment regimens combined.

2 Statistical Methodology

2.1 General Considerations

The objective of this study is to evaluate the safety and efficacy of TP-03, 0.25%, for the treatment of MGD in participants with Demodex lid infestation. Efficacy outcomes will include:

- Total meibomian gland secretion score (MGSS) computed as the sum of the grades for all 15 glands evaluated on the lower eyelid with a range from 0 to 45

[redacted]

- Lid margin erythema with a range of 0-3

[redacted]

Safety will be determined by assessing adverse effects related to treatment [redacted]

A subject is considered enrolled if they were dispensed drug. [redacted]

All statistical analyses will be performed using SAS Version 9.4 or higher. The sample size, mean, median, range and standard deviation will be presented for continuous analysis variables. Categorical variables will be presented as the count and percentage for each category. Statistical tests will be two-sided and evaluated at an α of 0.05 unless otherwise specified. Non-parametric tests will be utilized if warranted. No adjustment will be made for multiplicity.

2.2 Subject Population

2.2.1 Sample Size Justification

There is no prior data available for TP-03 in the treatment of MGD to use as a performance estimate. The sample size of 40 participants was selected based on

clinical and practical considerations. Results from this study will be used to inform the design of subsequent studies to demonstrate a therapeutic effect.

[redacted]

2.2.3 Randomization/Masking

2.2.3.1 Randomization Methodology

This is a randomized 1:1, double-masked study. A blocked randomization schedule will be prepared and used to package the afternoon dose of the drug (all subjects receive TP-03 for the morning and evening doses). [redacted]

2.2.3.2 Masking

The TP-03 vehicle will be used to maintain masking of the BID dosing. [redacted]

2.2.4 Study Populations for Analysis

The following are the analysis populations:

2.2.4.1 Intent to Treat (ITT) Population

The ITT Population will include all subjects randomized. In the event of a study drug administration error, analyses on the ITT Population will be performed according to the treatment the subject was planned to receive.

2.2.4.2 Safety Population

The Safety Population will include all subjects who received any amount of study drug. In the event of study drug administration error, analyses on the Safety Population will be performed according to the treatment the subject received.

2.2.5 Baseline Characteristics/Medical History

Sex, women of childbearing potential (WOCBP), age (in years), race, and ethnicity will be summarized for all subjects included in the ITT and safety populations by dosing regimen and overall.

Medical and ocular history will be coded using MedDRA and will be summarized by PT and SOC for all subjects included in the safety populations by dosing regimen and overall.

2.2.6 Subject Disposition

All subjects enrolled into the study will be accounted for in Subject Disposition. The numbers and percentages of subjects who are enrolled, who comprise each of the analysis populations and who complete the study or withdraw prematurely along with the reason for discontinuation will be tabulated by dosing regimen and overall. The number of subjects who were seen at each specified study visit will also be tabulated by dosing regimen and overall.

Protocol deviations will be classified by major or minor and approved by the medical monitor and will be tabulated by dosing regimen and overall.

2.2.7 Methods for Handling Missing Data

Missing data will not be imputed.

2.2.8 Efficacy Analyses

The primary efficacy analyses will be conducted on the ITT Population. Efficacy analyses for ocular measures will be performed for the analysis eye [redacted] Efficacy analyses will be performed as described below:

<u>Total meibomian gland secretion score (MGSS)</u>
Each gland will be graded on a scale of 0 (no secretion) to 3 (clear liquid secretion). Total score will be calculated as a sum of the grades of all 15 glands for the analysis eye per subject (range 0-45). [redacted]
Change from baseline will be calculated [redacted]

[redacted]. P-values will be calculated comparing the change from baseline at each visit between the two dosing regimens using a two-sided two-sample t-test.

[redacted]

Lid margin erythema

Erythema of the lid margins will be assessed using an ordinal grading scale from 0 (normal) to 3 (severe erythema) i[redacted] P-values will be calculated comparing the two dosing regimens using a Wilcoxon rank sum test. [redacted]

[redacted]

[redacted]

2.2.8.1 Hypothesis Testing

For the comparison analysis between dosing regimen groups for the efficacy outcomes the null hypothesis is that the efficacy outcomes for the dosing regimens are equal. The alternative hypothesis is the efficacy outcomes are not equal, i.e., a two-sided test. The hypothesis can be expressed as follows:

$$H_0: E_1 = E_2$$
$$H_A: E_1 \neq E_2$$

where E_1 and E_2 are the efficacy outcomes for each dosing regimen.

For the analyses of the change from baseline in efficacy outcomes within each dosing regimen and combined, the null hypothesis is there is no difference between the baseline and follow-up values. The alternative hypothesis is the follow-up outcome has improved from baseline. The hypothesis can be expressed as follows:

$$H_0: D \leq 0$$
$$H_A: D > 0$$

where D is the improvement from baseline

Note for measures where an improvement from baseline would be a decrease from the baseline score these hypotheses are inverse.

$$H_0: D \geq 0$$
$$H_A: D < 0$$

where D is the improvement from baseline

2.2.9 Safety Analyses

Safety analyses will be conducted on the Safety Population. Only descriptive statistics will be presented; inferential statistical testing will not be performed.

2.2.9.1 Adverse Events

Counts and percentages of subjects who experienced any of the following will be presented: any AE, any drug-related AE, discontinuations of study treatment due to an AE, discontinuations of study participation due to an

AE, any serious adverse events (SAE), deaths, or drug-related SAEs by dosing regimen and overall. Only those adverse events determined to be treatment emergent (TEAE) will be presented. Treatment emergent adverse events are those events with the date of AE onset being greater than or equal to the first date of dosing. Ocular AEs will be tabulated separately from non-ocular AEs for both TEAEs and SAEs.

Verbatim terms on the case report forms will be linked to preferred terms and related body systems using the MedDRA Coding Dictionary version xx (to be updated at time of DBL) The number and percentage of subjects who experience treatment-emergent adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT). Adverse events will be counted only once for a subject within each Preferred Term and System Organ Class; thus, since a subject may have more than one Preferred Term within an SOC, percentages of PT may not sum to the percentage in the SOC. If a subject reports a Preferred Term multiple times with differing severities, only the most severe is counted. If a subject reports a Preferred Term multiple times with differing relationships to study medication, only the one related to study drug is counted. Drug-related adverse events are defined as having a causality rating of definitely or potentially related.

AEs will also be tabulated by severity of the event (mild, moderate or severe) and by Investigator's assessment of relationship to study medication (Definitely related, potentially related or not related). Adverse events judged by the Investigator to be Serious Adverse Events (SAEs), SAEs resulting in death, AEs (regardless of seriousness) that require modification to Study Medication dosing will also be tabulated by SOC and PT by dosing regimen and overall.

2.2.9.1.1 Serious Adverse Events

The number and percentage of subjects experiencing a Serious Adverse Event (SAE) will be tabulated by SOC and PT by dosing regimen and overall. SAEs will be counted only once for a subject within each PT and SOC.

2.2.9.1.2 Deaths

Subjects who die while on study will be presented in a listing along with the adverse event associated with the cause of death.

2.2.9.1.3 Interruptions or Discontinuations of Study

Subjects who require study medication dosing changes due to an Adverse Event will be presented in a listing.

[redacted]

2.2.9.3 Prior and Concomitant Medications & Therapies

All concomitant medications including over-the-counter medications and nutritional supplements used within 3 months prior to the first visit will be documented. Any changes to concomitant medication use or initiation of new medications will be reported throughout the study. Concomitant Medications will be coded per the WHO Drug dictionary (version effective B3 September, 2021). Prior and concomitant Medications will be tabulated by Drug Class (pharmacological level, ATC3) and Drug Name (chemical substance level, ATC5) by dosing regimen and overall. These data will be provided in subject data listings along with the verbatim drug term and usage details. Any prohibited concomitant medications used by participants indicated in the protocol in Section 15.1 will be provided in a separate subject data listing if applicable.

[redacted]

3 Document Version Control

Revision History:

REVISION	RELEASE DATE	AUTHOR	SUMMARY OF CHANGES