STATISTICAL ANALYSIS PLAN

Clinical Investigation Title:	Comparison of the performance and safety of T2769 versus Vismed® Multi in the treatment of moderate to severe Dry Eye Syndrome
Clinical Investigation Plan (CIP) No.:	LT2769-002
CIP Version/Date:	Version 2.0 dated 15 06 2023
Investigational Medical Device (IMD):	T2769
Sponsor:	Laboratoires Théa Research and Development Department [redacted]
Statistical Analysis Plan (SAP) Version/Date:	Version 1.0, 13 September 2024

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
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LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse Event
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
CI	Confidence Interval
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
[redacted]	[redacted]
CRO	Contract Research Organization
D	Day
DES	Dry Eye Syndrome
DSMB	Data Safety Monitory Board
eCRF	electronic Case Report Form
FAS	Full Analysis Set
IMD	Investigational Medical Device
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
[redacted]	[redacted]
LS	Least Square
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NaCl	Sodium Chloride
[redacted]	[redacted]
PT	Preferred Term
PP	Per Protocol
Q1	First Quartile
Q3	Third Quartile
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
USADE	Unanticipated Serious Adverse Device Effect
[redacted]	[redacted]
WHODrug	World Health Organisation Drug

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the clinical investigation with Clinical Investigation Plan (CIP) No. LT2769-002, version 2.0 dated 15.06.2023 (LT, 2023).

This SAP is based on the electronic Case Report Form (eCRF) version 4.0 dated 29.05.2024.

The analyses follow the guidelines from the International Organization for Standardization (ISO) described in ISO 14155 Clinical investigation of medical devices for human subjects -- Good clinical practice (ISO 14155).

The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Investigation Report (CIR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the investigation is to demonstrate the non-inferiority of T2769 versus Vismed® Multi in terms of total ocular surface staining (Oxford score) in patients with Dry Eye Syndrome (DES), after 35 days of treatment.

[redacted]

2.2 Study Design

2.2.1 Overview

This investigation consists in a 5-week, international, multicentre, randomised, investigator-masked, 2-parallel-group (T2769 versus Vismed® Multi) confirmatory clinical investigation, planning to randomise 250 patients.

The investigation period for a patient is split into two parts, with a total maximum duration of 49 days:

- 7 to 10 days of run-in period with preservative-free artificial tears (Hydrabak®, NaCl 0.9%)
- 36 to 39 days of treatment period with the Investigational Medical Device (IMD): either T2769 or Vismed® Multi.

Four visits are scheduled during the course of the investigation:

- Visit #1: Day 1-10/Day 1-7: Screening visit (run-in period)
- Visit #2: Day 1: Randomisation visit (D1)
- Visit #3: Day 15 (±1 day): (D15)
- Visit #4: Day 36 (+3 days): Final or premature discontinuation visit.

The detailed Schedule of Visits and Procedures is described in Table 2 of the CIP [redacted]

2.2.2 Randomisation and Masking

Patients are randomised stratified by site on a 1:1 basis to T2769 or Vismed® Multi respectively. The randomisation code list and the lists of IMDs numbers for the packaging is generated by the Interactive Web Response System (IWRS) provider, the randomisation and the IMD kits numbers are allocated to the patients according to randomisation list using an Interactive Response Technology (IRT).

Randomisation occurs at Randomisation visit (Day 1; Visit #2) after all procedures have been performed and eligibility for the investigation confirmed.

This is an investigator-masked clinical investigation, a double-masked investigation design not being possible due to different commercial packaging between T2769 and Vismed® Multi.

The masked investigator remains masked to the IMD (T2769 or Vismed® Multi). The masked investigator does not receive the returned IMDs from the patients.

The following-up of returned IMDs is delegated to an unmasked collaborator throughout the clinical investigation. The unmasked collaborator is in charge of recording the used/unused IMDs.

Masking is achieved by coding the interventions, providing each product unit with identical cardboard box and by identifying it by an IMD kit number.

The code should not be broken except:

- in case of medical emergency (where knowledge of the IMD received would affect the treatment of the emergency),
- or when it is a regulatory requirement (e.g., for Unanticipated Serious Adverse Device Effect [USADE]).

The investigator is responsible for accessing the IRT system to obtain the name of the IMD received by the patient.

If an emergency code breaking becomes necessary, the investigator should notify the Sponsor.

When a code is broken, the date, time and reason must be recorded in the patient's source, and in any associated Adverse Event (AE) report. The identity of the IMD should not be disclosed in these documents.

Further to an USADE assessment by the Global Drug Safety & Medical Information Department, the code might be broken for reporting purposes. The relevant Laboratoires Théa, Contract Research Organization (CRO), masked investigator and masked staff remain unaware of the identification of the IMD as per the above-mentioned process.

The overall randomisation list will be broken for data analysis after database lock.

2.2.3 Hydrabak® and Investigational Medical Device

The dose regimen of Hydrabak® and of the IMD is 1 drop in each eye, from 3 to 6 times daily, and the route of administration is topical, ocular use.

2.2.4 Sample Size Determination

The sample size is driven by the statistical hypotheses on the primary [redacted] endpoint[redacted]

[redacted]

2.3 Study Endpoints

2.3.1 Primary Performance Endpoint

The primary performance endpoint is the change from baseline (D1) in total ocular surface staining assessed on Oxford 0-15 scale, in the study eye at the D36 visit.

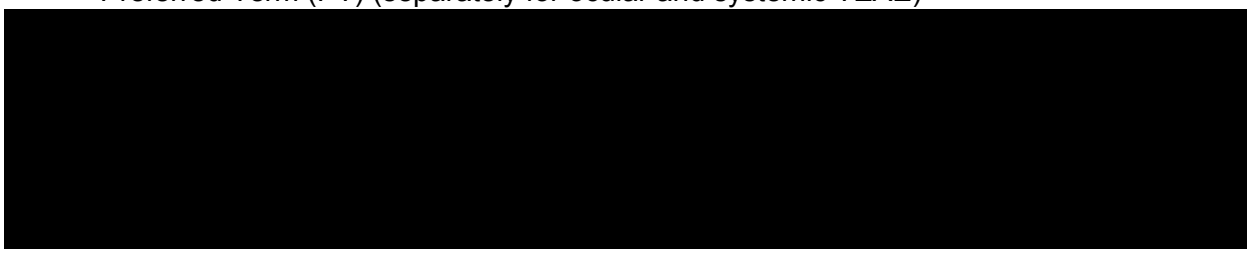
Baseline is defined in section 3.1.3 [redacted]

[redacted]

2.3.3 Safety and Tolerability Endpoints

The safety endpoints are:

- Treatment Emergent Adverse Event (TEAE) by System Organ Class (SOC) and Preferred Term (PT) (separately for ocular and systemic TEAE)



3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

The day of randomisation will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

[redacted]

3.1.3 Definition of Baseline

Baseline is defined as the assessment at randomisation visit (D1) before the first IMD instillation.

Missing value at randomisation visit (D1) will not be replaced.

The change from baseline at a given visit is defined as the difference between the assessment at the given visit and the baseline.

[redacted]

[redacted]

3.1.5 Summary Statistics

Categorical data will generally be summarized with number of non-missing observations (n), counts and percentages of patients in each modality. Associated two-sided 95% CI for proportions will be calculated using the scoring method of Wilson without continuity correction. The missing values will not be counted for the percentage calculation.

Continuous data will generally be summarized with mean (with associated two-sided 95% CI), median (with associated two-sided 95% CI), standard deviation (SD), lower quartile (Q1), upper quartile (Q3), minimum, and maximum.

Generally, the minimum and maximum values will be reported to the same number of decimal places as the original values. The mean, median, quartiles and CIs will be reported to one additional decimal place, and the SD will be reported to two additional decimal places.

For endpoints defined as change from baseline, descriptive statistics and the change from baseline will be presented by visit.

Parameters recorded for both eyes will be described separately for the study eye and for the contralateral eye.

[redacted]

[redacted]

3.1.7 Handling of Missing Data

3.1.7.1 Missing Data Handling for Primary [redacted] Endpoint

For the primary performance endpoint analysis performed on FAS, Mixed Model for Repeated Measures (MMRM) method will be applied. MMRM method assumes missing data are Missing at Random (MAR) and no explicit imputation of missing assessments for a given visit time point will be performed. [redacted]

[redacted]

[redacted]

3.2 Analysis Sets

3.2.1 Enrolled Set

All patients who have signed the informed consent form and for whom the inclusion visit has been recorded in the eCRF.

3.2.2 Safety Set

All enrolled patients, having received at least one dose of IMD and analysed as treated.

The safety set will be the primary population for safety analysis.

3.2.3 Intent-To-Treat (ITT) Set

All randomised patients and analysed as randomised.

3.2.4 Full Analysis Set (FAS)

All randomised patients, having received at least one dose of IMD, with at least one baseline and one post-randomisation performance assessment and analysed as randomised.

The FAS will be the primary population for performance analysis.

3.2.5 Per Protocol (PP) Set

Subset of the FAS including patients without any major CIP deviations likely to seriously affect the primary [redacted] outcome [redacted] of the study [redacted]

Deviations from the CIP will be defined and assessed as “minor” or “major” in cooperation with the Sponsor during a blind review meeting before the database lock. A list of patients with major deviations from the CIP leading to exclusion from the PP set will be finalized prior to unblinding the randomised treatment assignments.

The PP set will be considered as secondary population and will be used for sensitivity analyses of the primary [redacted] endpoint. Patients will be analysed as treated.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened (signed informed consent), terminated prematurely during screening (screen failures), received run-in treatment, completed run-in period, and randomised will be summarized in total based on all screened patients.

Counts and percentages of patients in each of the following categories will be presented by treatment arm and in total for the ITT set, FAS and PP set:

- Patients who were randomised

- Patients who received IMD
- Patients who completed the treatment period
- Patients who early discontinued the treatment period
- Patients who completed the study
- Patients who early discontinued from the study

Summary will also be provided for the Safety set [redacted]

For patients who discontinued early from treatment and from the study, primary reasons for premature discontinuation will also be summarized.

A summary of the number of patients who attended each scheduled visit will be presented.

Corresponding listings for disposition and visit attendance be produced.

[redacted]

3.3.3 Analysis Sets

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on the ITT set. Reasons for exclusion from the PP set will also be summarized.

Corresponding listing for analysis sets will be produced.

3.3.4 Demographic and Baseline Characteristics

The following demographic characteristics will be summarized by treatment and in total for the ITT set, the FAS and the PP set:

- Age at screening (in years)
- Age category (at screening)
  - < 65 years
  - >= 65 to < 85 years
  - >= 85 years
- Sex (female, male)

[redacted]

The following history of dry eye disease will be summarized by treatment and in total for the ITT set, the FAS and the PP set:

- localisation (one eye, both eyes),

- time from first diagnosis to randomisation (in years): [redacted]

[redacted]

3.3.5 Medical History

Medical history data are coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher. Counts and percentages of patients with medical history by SOC and PT will be summarized by treatment and in total based on the Safety set, separately for ocular and systemic (non-ocular) [redacted]

3.3.6 Historical Surgeries/Procedures

Historical surgeries and procedures are coded to SOC and PT using the MedDRA version 26.0 or higher. Counts and percentages of patients with historical surgeries and procedures by SOC and PT will be summarized by treatment and in total based on the Safety set, separately for ocular and systemic (non-ocular) [redacted]

3.3.7 Prior and Concomitant Medications

Prior and concomitant medications are coded to Anatomical Therapeutic Chemical (ATC) class and PT using the World Health Organisation Drug (WHODrug) dictionary (version Mar 2023G B3). [redacted]

[redacted]

3.3.8 Study Medical Device Exposure and Compliance

The extent of exposure and compliance of patients to IMD will be summarized by treatment group for the FAS, PP set and Safety set [redacted]

Counts and percentages of patients treated for one single eye and for both eyes will be summarised.

[redacted]

IMD administration and compliance data will be listed.

3.4 Performance Assessment

The FAS will be the primary population for performance analysis. The PP set will be considered as secondary population and will be used for sensitivity analyses of the primary endpoint [redacted]

For primary [redacted] performance endpoint[redacted], descriptions will be given by treatment group at each assessment time. Change from baseline will be also presented, when applicable.

When using inferential analysis, Least Square (LS) means and its standard errors will be displayed for each treatment group. The LS means for the difference (T2769 - Vismed® Multi) between the treatment groups' change from baseline, its two-sided 95% CI and the p-value, when applicable, will be provided.

3.4.1 Primary Performance Endpoint

The primary objective is to demonstrate the non-inferiority of T2769 compared to Vismed® Multi in terms of total ocular surface staining (Oxford score) after 35 days of treatment. The primary

performance endpoint is the change from baseline (D1) in total ocular surface staining assessed on Oxford 0-15 scale, in the study eye at the D36 visit. [redacted]

Primary Analysis

The inferential analyses of the primary performance endpoint will aim to assess the non-inferiority of T2769 to Vismed® Multi.

The hypothesis of non-inferiority of T2769 compared to Vismed® Multi will be tested by calculating the bilateral 95% CI of the difference between groups (T2769 – Vismed® Multi) of the total ocular surface staining (Oxford score) at D36 in the study eye in the FAS.

The non-inferiority of T2769 to Vismed® Multi on the total ocular surface staining (Oxford score) will be primarily tested using an MMRM approach.

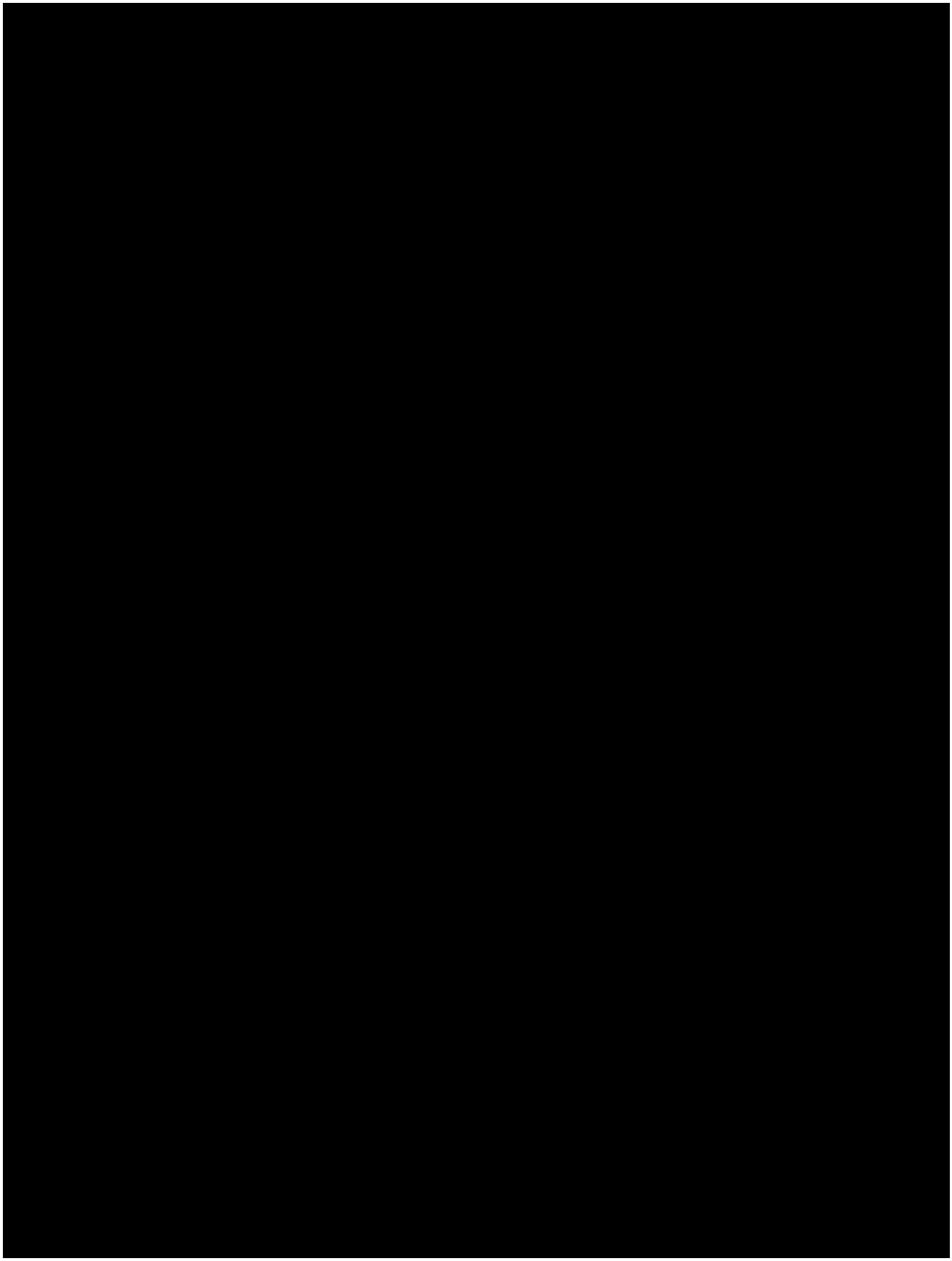
The model will include treatment and scheduled visit time points (D15 and D36) as fixed factors, patient as random factor, and baseline total ocular surface staining (Oxford score) as continuous covariate. Treatment by scheduled visit time point and baseline total ocular surface staining (Oxford score) by scheduled visit time point will be included as interaction terms in the model. [redacted]

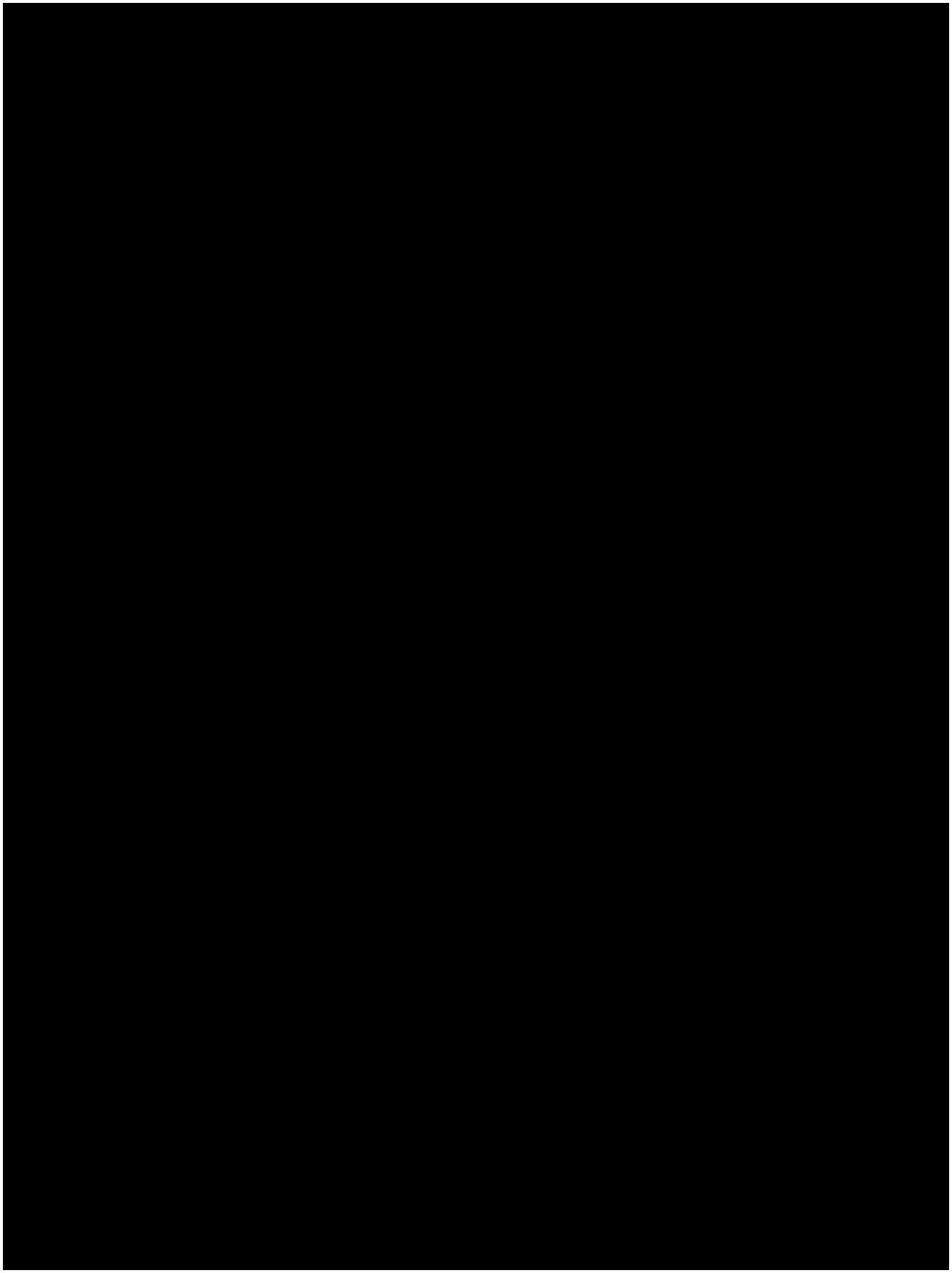
LS means and corresponding standard errors for change from baseline at each analysis visit will be provided for each treatment group. The difference in LS means between T2769 and Vismed® Multi, corresponding standard error, and the two-sided 95% CI for treatment effect (difference T2769 - Vismed® Multi) will be estimated at each analysis visit in this model. Non-inferiority will be achieved if the upper bound of the two-sided 95% CI for the difference between treatment groups (T2769 - Vismed® Multi) at D36 is lower than the margin of 2 points.

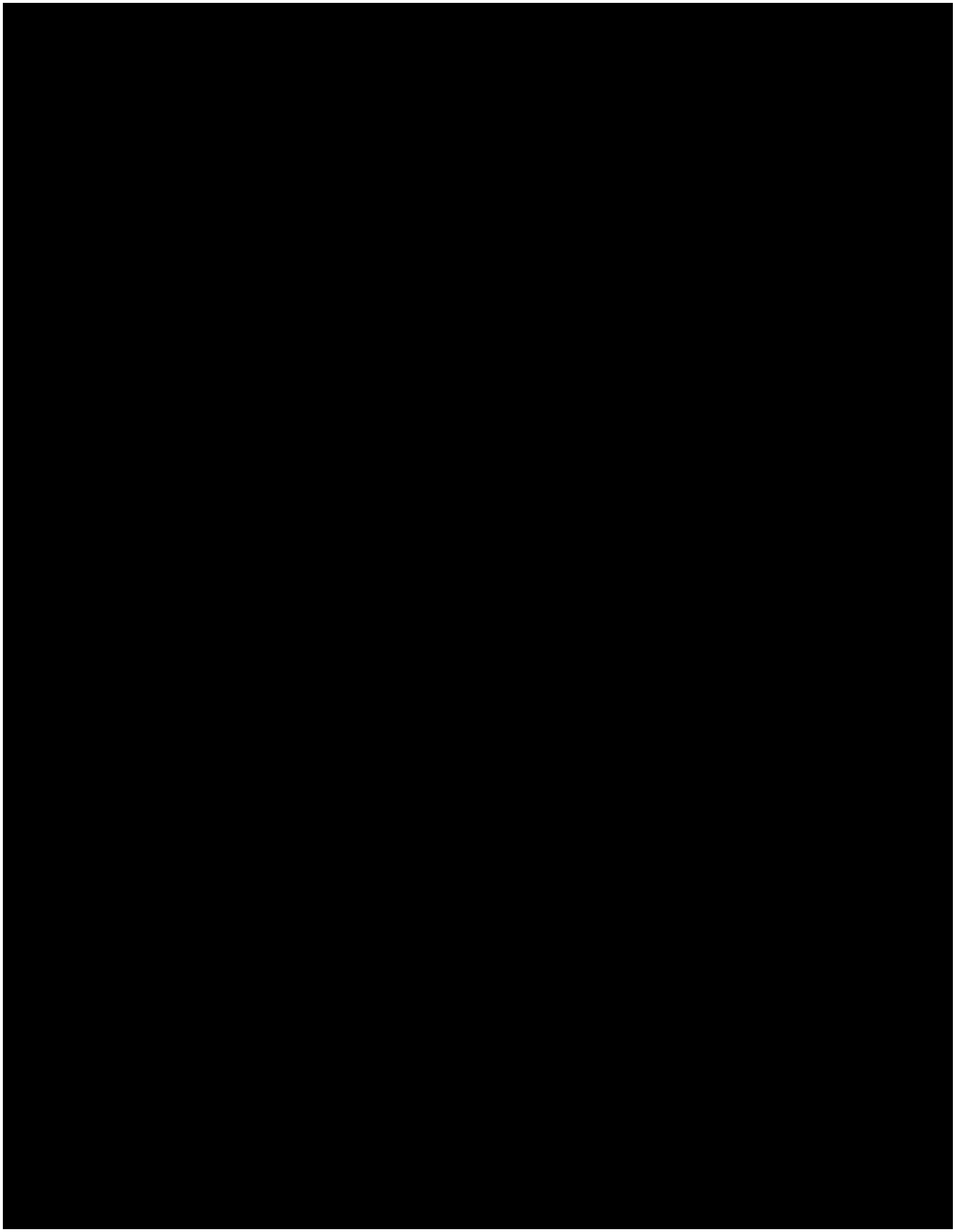
Descriptive summary statistics on the values and changes from baseline will be presented for the total ocular surface staining (Oxford score) at each analysis visit by treatment group.

The mean and associated SD of the Oxford score in the study eye will be graphically displayed for each treatment by analysis visit in the FAS.

[redacted]







3.5 Safety Assessment

Safety endpoints will be analysed in the Safety set.

3.5.1 Adverse Events (AEs)

Ocular and systemic AEs reported during the investigation will be coded using the MedDRA dictionary version 26.0 or higher.

Treatment-Emergent Adverse Event

An overview of TEAEs by treatment groups, separately for ocular and systemic TEAEs, will be provided for each of the following TEAE categorizations, in terms of the count and percentage of patients experiencing at least once such a TEAE:

- Any TEAE
- Any Serious TEAE
- TEAE leading to premature IMD discontinuation
- IMD-related TEAE
- IMD-related serious TEAE

A summary table by treatment groups, separately for ocular and systemic TEAEs, will be presented for each of the following TEAE categorizations, in terms of the count and percentage of patients experiencing at least once such a TEAE, as well as the number of TEAEs by SOC and PT:

- TEAEs leading to premature IMD discontinuation
- TEAEs by severity (Mild/Moderate/Severe/Missing if any)
- TEAEs by relationship to IMD (Not Related/Missing, if any/Possible/Probable/Causal Relationship)
- Serious TEAEs by relationship to IMD

A summary table by treatment groups, for ocular and systemic AEs altogether, will be presented for each of the following AE categorizations, in terms of the count and percentage of patients experiencing at least once such an AE as well as the number of AEs by SOC and PT:

- Any Non-Serious TEAE
- Any Non-Serious TEAE, with PT occurring for at least 5% of the patients in any of the treatment groups
- Any Serious AE

Listings will be presented specifically for TEAEs, separately for ocular and systemic TEAEs.

[redacted]

4 DATA SAFETY MONITORING BOARD

No Data Safety Monitory Board (DSMB) is planned for this study.

5 ANALYSIS TIMING

5.1 Draft Analysis/Blinded Data Reviews

Draft analysis Tables, Figures, and Listings (TFLs) for blinded data reviews will be provided prior to the scheduled database lock for final review.

5.2 Interim Analysis

No interim analysis is planned.

[redacted]

[redacted]

6 CHANGES FROM CIP-SPECIFIED STATISTICAL ANALYSES

The following changes from the protocol-specified statistical analyses have been made:

[redacted]

- Addition of the Enrolled set

[redacted]

- Individual patient data listings, separately for ocular and systemic AEs, are not provided for SAEs and IMD-related SAEs.

[redacted]

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using [redacted]. Detailed Programming Specifications will be provided in a separate document. All Derived Datasets and TFL programs will be validated according to [redacted] SOP [redacted]

[redacted]