# SPONSOR:

Laboratoires Théa

# PROTOCOL NUMBER:

LT2769-003

# STATISTICAL ANALYSIS PLAN

NCT Number: NCT05931861

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| **Author:** | PPD |

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| **Sponsor:** | Laboratoires Théa |
| **Protocol Number:** | LT2769-003 |
| **Study Title:** | Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms |

**We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.**

***Lead Biostatistician***

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# Table of Contents

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# 1 Document History

| Date | Version | Author(s) | Brief details of changes made |
|---|---|---|---|
| 11SEP2023 | Draft 1 | PPD | Initial draft version sent to Laboratoires Théa |
| 02OCT2023 | Draft 2 | | Updated version after comments of Sponsor |
| 26OCT2023 | V1.0 | | Updated version after comments of Sponsor |

# 2 List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BCVA | Best Corrected Visual Acuity |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan |
| CIR | Clinical Investigational Report |
| CLDEQ | Contact Lens Dry Eye Questionnaire |
| CRF | Case Report Form |
| DED | Dry Eye Disease |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| IMD | Investigational Medical Device |
| ISO | International Organisation for Standardisation |
| LOCF | Last Observation Carried Forward |
| MDR | Medical Device Regulation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OSDI | Ocular Surface Disease Index |
| PPS | Per Protocol Set |
| PT | Preferred Term |
| Q1 | Lower Quartile |
| Q3 | Upper Quartile |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |

| | |
|---|---|
| TBUT | Tear Break Up Time |
| TFL | Tables – Figures – Listings |
| VAS | Visual Analog Scale |
| WHO-DD | World Health Organization-Drug Dictionary |

# 3 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in the analysis of the study titled Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms. This study, set up by Laboratoires Théa, aims to evaluate the performance and safety of T2769 in contact lens wearers with dry eye symptoms.

This Statistical Analysis Plan (SAP) covers the final analysis of the study. The list of tables, figures and listings (TFLs) to be developed, as well as the shells for each TFL, are presented in a separate document.

The preparation of this SAP has been based on study protocol version 1.0 from 04MAY2023, the latest available case report form (CRF) version 2.1 from 08SEP2023 and on International Organisation for Standardisation (ISO) 14155: 2020-Standard and on Medical Devices Regulation (MDR): 2017/745.

# 4 Study Description

## 4.1 Study Objectives and Endpoints

Below are the primary and secondary objectives along with the associated endpoints as per the study protocol.

**Table 1: Summary of objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the performance of T2769 in contact lens wearers with dry eye symptoms in terms of change from baseline (Day 1) to Day 36 (Final visit) in Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) total score. | • Change from baseline (D1) to D36 (Final visit) in CLDEQ-8 total score*. |

| Objectives | Endpoints |
|---|---|
| Secondary | |
| • To assess the performance of T2769 in contact lens wearers with dry eye symptoms. | • Change from baseline (D1) in CLDEQ-8 total score* at D15.<br>• Soothing sensation just after instillation (less than 5 minutes)* at D15 and D36.<br>• Change from baseline in Ocular Surface Disease Index (OSDI)* total score at D15 and D36.<br>• Change from baseline (D1) in the ocular discomfort score on the Visual Analog Scale (VAS)* at D15 and D36.<br>• Score of each ocular symptom throughout the day* (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation) at D15 and D36 and change from baseline in the total score of these symptoms.<br>• Change from baseline in contact lens wearing time at D15 and D36.<br>• Change from baseline in conjunctival hyperaemia score at D15 and D36 separately in the studied eye and in the contralateral eye.<br>• Change from baseline in Tear Break Up Time (TBUT) at D15 and D36 separately in the studied eye and in the contralateral eye.<br>• Change from baseline in total ocular surface staining grade according to Oxford 0-15 grading scheme at D15 and D36 separately in the studied eye and in the contralateral eye.<br>• Change from baseline in Schirmer test result (without anesthesia) at D15 and D36 separately in the studied eye and in the contralateral eye.<br>• Performance assessment by the investigator at D15 and D36.<br>**Patient questionnaire* |
| • To assess the safety of T2769 in contact lens wearers with dry eye symptoms. | • Treatment-Emergent Adverse Event (TEAE) by System Organ Class (SOC) and Preferred Term (PT) (separately for ocular and systemic TEAE).<br>• Change from baseline in Far Best Corrected Visual Acuity (BCVA) expressed in Log MAR at D36 separately in the studied eye and in the contralateral eye.<br>• Ocular tolerance assessed by the investigator at D15 and D36.<br>• Ocular tolerance assessed by the patient at D15 and D36. |

## 4.2 Study Design and Target Population

This is a prospective, single-arm, multicenter (in European Union), 5-week investigation. A total of CCI evaluable patients (adults wearing any type of contact lens) are expected in the study. Accounting for a 10% drop-out/non evaluable rate, CCI patients are expected to be enrolled.

Three visits are scheduled during the course of the clinical investigations for a total maximum investigation duration of 39 days:

- Visit #1: Day 1 Inclusion visit (D1)
- Visit #2: Day 15 (±1 day) (D15)
- Visit #3: Day 36 (+3 days) Final visit (D36)

All visits must take place in the afternoon.

## 4.3 Study Treatments and Procedures

**Study Treatment**

There is one group of investigational medical device (IMD):

- T2769: Sodium hyaluronate (0.15%), Trehalose (3%), N-Acetyl Aspartyl Glutamic Acid Sodium salt (Naaga, 2.45%), sodium hydroxide (for pH adjustment) and water for injections in a 12.5 mL ABAK® multi-dose bottle.

IMD is administered by the patient every day for 36 + 3 days, one drop in each eye 3 to 6 times daily (at any time during the day, but only when wearing their contact lenses), into the lower conjunctival sac of each eye.

No IMD instillation should be performed at least 2 hours before Visit #2 and #3. However, the first instillation could be done any time after the patient has completed the inclusion visit.

There is only 1 treatment group, all patients instil T2769.

**Procedures**

Schedule of assessments and procedures is presented in Section 1.4 of the protocol.

## 4.4 Randomisation and Blinding

Not Applicable.

## 4.5 Sample Size Determination

This is a confirmatory clinical investigation. The objective is to collect new additional clinical data demonstrating the safety and the performance of the device in the contact-lens wearing population with dry eye symptoms. Consequently, no formal sample size calculation is performed, and it is considered that around evaluable CCI patients is sufficient to reach the clinical investigation objectives.

A total of CCI patients should be enrolled in the study to take into account approximately 10% of drop-out/non-evaluable patients. Evaluable patients will be defined as included patients having received at least one dose of IMD and at least one evaluation of performance.

# 5 Considerations for Statistical Analysis

The *SAS Viya 3.5 (SAS Studio 5.2 or higher)* will be used for all analysis, unless otherwise specified.

## 5.1 Analysis Periods

**Visit Windowing**

All data will be analysed according to the planned visit as collected in the electronic CRF (eCRF).

Data from premature discontinuation visit will be allocated to the next planned visit unless the scheduled visit is performed after discontinuation visit.

## 5.2 Data Derivations

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**Baseline and Change from baseline**

Baseline and change from baseline will be calculated for all assessments as follows:

- Baseline value is defined as the assessment at inclusion visit before the first IMD instillation. Missing value at inclusion visit will not be replaced.

- Change from baseline will be calculated as the difference between the assessment value and the baseline value.
- Change from baseline in classes will be defined as follows in three classes compared to 0:
  - Improvement (Decrease of score from baseline): Change from baseline < 0,
  - Stable: Change from baseline = 0,
  - Worsening (Increase of score from baseline): Change from baseline > 0.

**Study Day**

Study day will be calculated as (assessment date - date of first IMD) for pre-baseline assessments and [(assessment date - date of first IMD) + 1] for post-baseline assessments, e.g., there will be no study day 0 and study day 1 will correspond to the first IMD.

**Age**

Age (years) will be calculated in classes as: < 65, ≥ 65 and < 85, ≥85 years.

**Time since DED diagnosis**

Time since DED diagnosis (months) will be calculated as (Date of inclusion visit - Date of diagnosis) / 365.25 x 12.

If the day is missing and month is present the 15 of the month will be used. If year is present and day and month are missing, the time since DED diagnosis will be calculated as (Year of inclusion visit - Year of diagnosis) x 12.

**Duration of exposure**

Duration of exposure (days) will be calculated as (Date of last instillation - Date of first instillation) + 1.

If the day or the month is missing for one of the dates, the duration of exposure will be missing.

**Number of days with instillation of T2769**

Number of days with instillation will be calculated for both eyes together as follows:

- From D1 to D15: (Date of Visit #2 - Date of inclusion Visit + 1) - (Number of days without instillation of IMD recorded in the eCRF at Visit #2).
- From D15 to D36: (Date of Visit #3 - (Date of Visit #2 + 1) + 1) - (Number of days without instillation of IMD recorded in the eCRF at Visit #3).
- From D1 to D36: Sum of number of days with instillation from D1 and D15 and from D15 and D36.

**CLDEQ-8 total Score**

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**OSDI**

CCI

**Total score of ocular symptoms throughout the day**

CCI

**Mean contact lens wearing time as mean number of days/week**

CCI

**TBUT**

CCI

**Total ocular surface staining grade**

CCI

**Far BCVA**

CCI

**Adverse event (AE) time to occurrence**

Time to AE occurrence (days) will be calculated as Date of onset – Date of IMD instillation.

**AE duration**

Duration (days) of an AE will be calculated as (Date of recovery – Date of onset) + 1.

## 5.3 Other Data Analyses Considerations

**Strata and Covariates**

Not Applicable.

**Multiple Comparisons and Multiplicity**

There is a single primary performance endpoint in the study (change from baseline to D36 in the CLDEQ-8 total score). Other performance measures are defined as of secondary importance. Thus comparison will be performed at a two-sided significance level of CCI; no adjustment of the type I error rate will be made.

# 6 Analysis Sets

Analysis sets to be used for the analyses are described in the table below.

**Table 1: Analysis Sets**

| Analysis Set | Description |
|---|---|
| Enrolled set | All patients who have signed the informed consent form and for whom the inclusion visit has been recorded in the eCRF. |
| Safety set | All enrolled patients, having received at least one instillation of IMD.<br>The safety set will be the primary population for the safety analysis. |
| Full-Analysis set (FAS) | All enrolled and included (i.e., started the treatment period) patients, having received at least one instillation of IMD and with at least one baseline and one post-baseline performance assessment.<br>The FAS will be the primary population for the performance analysis. |

| Analysis Set | Description |
|---|---|
| Per-protocol set (PPS) | Subset of the FAS including patients without any major clinical investigation plan (CIP) violations likely to seriously affect the primary outcome of the study.<br>Deviations from CIP will be detailed in a separate document and assessed as "minor" or "major" during data review meeting before the database lock.<br>The PPS will be considered as a secondary population and will be used for sensitivity analyses of the primary and secondary endpoints. |

# 7 Methods of Analysis

## 7.1 General Considerations

Statistical analyses will be performed by the Biostatistics unit of CCI Analyses will be conducted with SAS Studio 5.2 under SAS Viya 3.5 (SAS Institute, North Caroline, USA).

Continuous data will be described in summary tables presenting, overall, the number of non-missing observations (n), mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% Confidence Interval (CI) of the mean/median.

Categorical data will be described in summary tables presenting, overall, the number of non-missing observations (n), count and percentage of each modality, and 95% CI.

95% CI of a proportion will be calculated using the scoring method of Wilson without continuity correction:

Lower Limit = $\frac{2np + z^2 - z\sqrt{z^2 + 4npq}}{2(n + z^2)}$ Upper Limit = $\frac{2np + z^2 + z\sqrt{z^2 + 4npq}}{2(n + z^2)}$

with n = number of non-missing observations

p = percentage

q = 1 - p

z = 1.96 for two-sided 95%CI

Except for minimum and maximum, descriptive statistics will be presented with one more decimal than the recorded value.

For all variables, the number of missing values will also be reported in the tables, but they will not be counted for the percentage calculation (categorical data).

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

The acceptable risk of error for the statistical tests will be set at 5%.

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Tables and Listings will be provided in separated documents (Word and PDF files) except the listing of Deaths, Other Serious Adverse Events, discontinuations due to Adverse Events and other Adverse Events of Special Interest (if applicable) which will also be provided in Excel format (see Section 7.10.1).

All individual data will be described in the patient data listings (CCI by patient as follows: discontinued patients, protocol deviations, patients excluded from the performance analysis, demographic data and baseline characteristics, compliance/exposure, individual performance response data, adverse events (AEs) listings.

## 7.2 Patient Disposition

Patient disposition data will be presented overall.

The number of enrolled patients will be presented overall. The number (%) of patients included in each other analysis set (Safety set, FAS and PPS) will be presented overall.

The number (%) of patients by centre will be presented overall, for FAS and PPS.

The number (%) of patients per visit as considered in the analysis (i.e., after remapping of the premature discontinuation visit) will be described overall for FAS and PPS.

A listing of patients with information on analysis sets and studied eye will be produced for the enrolled patients and a listing of actual visits and visits as considered in the analysis (see Section 5.1) will be produced for the FAS.

The number (%) of patients who prematurely discontinued the study and the primary reason for discontinuation will be presented overall for the Safety Set and FAS. The number (%) of patients who prematurely discontinued the IMD and the primary reason for discontinuation will be presented overall for the Safety Set and FAS. A listing will be produced on the Safety Set presenting the patients who prematurely discontinued the study or the IMD with the detailed reason for discontinuation.

A listing of patients excluded from FAS, PPS or Safety set, presenting the reason for exclusion, will be produced on the enrolled patients.

## 7.3 Protocol Deviations

The list of potential protocol deviations will be pre-defined in separate document.

Prior to data lock for analysis, a meeting will be held to review protocol deviation classification, and to agree on the analysis sets.

The number (%) of patients with at least one major deviation, the number (%) of patients with only minor deviations (without major deviations) and the number (%) of patients with minor deviations (including those with major deviations) will be presented overall for the FAS. The deviations will also be described for FAS and a listing with all minor/major deviations will be provided.

## 7.4 Demographics and Baseline Characteristics

The following demographic will be summarized using descriptive statistics and presented overall using the Safety Set, FAS and PPS:

- Demographics:
  - Age (years) as continuous and in three classes (< 65 / ≥ 65 and <85 / ≥85 years old),
  - Gender (Male / Female),
  - Gender by age class.

The following baseline characteristics will be summarized using descriptive statistics and presented overall using the FAS and PPS:

- Contact Lens History:
  - Contact lens type (Soft / Rigid gas permeable),
  - If soft contact lens type, replacement modality (Daily / Weekly / Bi-Weekly / Monthly / Every 3 months / Every 6 months / Yearly),
  - If not daily contact lens, contact lens solution type (Preserved / Not preserved),
  - History of contact lens intolerance (Yes / No).
- DED History:
  - Time since DED diagnosis (months) in the studied and the contralateral eyes.

Data regarding contraception status, effective method of contraception and pregnancy test results (for women) will be presented in an individual data listing CCI

Baseline values of the performance and safety endpoints will be provided in statistical tables with assessments at D15 and D36 (see Sections 7.8 and 7.10).

## 7.5 Medical History

Diagnosis (for medical history) and surgical procedures (for surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1, English or higher.

Number (%) of patients will be presented by SOC and PT using the FAS and PPS:

- Medical history:
  - Ocular medical history (included DED),
  - Systemic medical history.
- Surgical history:
  - Ocular surgical history,
  - Systemic surgical history.

## 7.6 Prior and Concomitant Medications

All previous and concomitant ocular and non-ocular treatments will be coded using World Health Organization-Drug Dictionary (WHO-DD) version Format C3, September 1, 2022 or higher.

Treatments will be summarised according to the Anatomical therapeutic chemical (ATC) class (level 2 and level 4) of the WHO-DD dictionary.

A previous treatment will be defined as a treatment stopped prior to (or the same day as) the first instillation of the IMD.

A concomitant treatment will be defined as a treatment i) started after (or the same day as) the first instillation of the IMD, ii) started prior to and continued after the first instillation of the IMD. If the classification is not possible due to partial start/end date(s) of treatment, the treatment will be considered as concomitant.

Number (%) of patients will be presented by ATC4 and ATC2 using the FAS and the PPS:

- Ocular treatments
  - Previous ocular treatments,
  - Concomitant ocular treatments.
- Non-ocular treatments
  - Previous non-ocular treatments,
  - Concomitant non-ocular treatments.

## 7.7 Treatment Exposure and Compliance

The following data on the use of the IMD will be summarized using descriptive statistics overall using the FAS and PPS:

- Treated eye (Right eye / Left eye/ Both eyes),
- Duration of exposure (days),
- Mean daily dose regimen (less than 3 / 3 instillations/day / 4 instillations/day / 5 instillations/day / 6 instillations/day and more then 6) at D15 and D36,
- Total number of days with study treatment (between D1 and D15, between D16 and D36 and between D1 and D36) for the studied eye and the contralateral eye separately.

## 7.8 Performance Analyses

Primary and secondary performance endpoints will be primarily analysed on the FAS. Sensitivity analysis of the primary and secondary performance endpoints will be performed on the PPS.

### 7.8.1 Primary Performance Objective

The primary performance endpoint is the change from baseline (D1) to D36 in the CLDEQ-8 total score.

Descriptive statistics will be performed at each assessment time (baseline, D15 and D36) overall. Change from baseline will be described as well.

**Main Analysis**

To assess the performance of T2769, on change from baseline (D1) to D36 in the CLDEQ-8 total score, estimate of the change and associated 95% CI will be provided, as well as p-value for the paired t-test. Analysis will be performed on observed cased (without imputation).

The syntax with SAS using the UNIVARIATE procedure is detailed in Section 11.2.

**Sensitivity Analyses**

The analysis of the primary performance endpoint will be repeated on the PPS.

### 7.8.2 Secondary Efficacy Objectives

Secondary performance endpoints will be analysed based on observed cased (without imputation) on the FAS and the PPS.

**CLDEQ-8 total score at D15**

Change from baseline to D15 in the CLDEQ-8 total score will be analysed using the paired t-test in the same way as for the primary endpoint.

**Soothing sensation at D15 and D36**

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**OSDI total score at D15 and D36**

CCI

**Ocular discomfort score on the VAS at D15 and D36**

CCI

**Ocular symptom throughout the day at D15 and D36**

CCI

**Contact lens wearing time at D15 and D36**

CCI

**Conjunctival hyperaemia score at D15 and D36**

CCI

**TBUT mean at D15 and D36**

CCI

**Total ocular surface staining grade at D15 and D36**

CCI

**Schirmer score (without anesthesia) at D15 and D36**

CCI

**Performance assessment by the investigator at D15 and D36**

Assessment of the IMD performance assessed by investigator on a 4-point ordinal scale (Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory) will be presented at D15 and D36 by frequency distribution for each modality.

## 7.9 Pharmacokinetic / Pharmacodynamic Analyses

Not Applicable.

## 7.10 Safety Analyses

All safety analyses will be performed using descriptive statistics overall using the Safety set, unless otherwise specified.

### 7.10.1 Adverse Events

Ocular and systemic AEs reported during the investigation will be coded using MedDRA dictionary version 26.1, English or higher.

Summary tables will be performed on Treatment-Emergent AEs (TEAEs).

Ocular and systemic TEAEs will be analysed separately on the basis of the localisation and System Organ Class (SOC), unless stated otherwise.

The following definitions will be used:

- Treatment-emergent AEs: AEs that occurred after the first IMD instillation. AEs that occurred the day of the first IMD instillation or AE with an incomplete date that make it impossible to determine whether it is a TEAE or not will be reviewed during a data review meeting to decide if they have to be considered as TEAE or not,
- Related AEs: AEs suspected by the Investigator to have a relationship to IMD (as recorded on the AE eCRF page, Causal relationship to IMD = Causal relationship, Probable related, Possibly Related, or missing),
- Serious AEs: serious AEs (as recorded on the AE eCRF page, Is a serious AE? = Yes, or missing),
- AEs leading to premature IMD discontinuation: AEs leading to premature IMD discontinuation (as recorded on the AE eCRF page, Action taken with IMD = IMD withdrawn),

**Summary of TEAEs**

Separate summaries of ocular and systemic TEAEs will be performed presenting the number and percentages of patients experiencing at least one:

- TEAE,
- Serious TEAE,
- IMD-related TEAE,
- IMD-related serious TEAE,
- TEAE leading to premature IMD discontinuation.

**Details of TEAEs**

Separate descriptions of ocular and systemic TEAEs will be performed:

- Number and percentage of patients experiencing at least one TEAE as well as the number of TEAEs by SOC and PT. The same summary table will be performed for Serious TEAEs and TEAEs leading to premature IMD discontinuation.
- Number and percentage of patients experiencing at least one TEAE as well as the number of TEAEs by SOC, PT and relationship with IMD. The same summary table will be performed for Serious TEAEs.
- Number and percentage of patients experiencing at least one TEAE as well as the number of TEAEs by SOC, PT and severity.

Three additional tables will be produced:

- Number and percentage of patients experiencing at least one non-serious TEAEs (ocular or systemic together), as well as the number of these TEAEs by SOC and PT
- Number and percentage of patients experiencing at least one non-serious TEAEs (ocular or systemic together) when percentages by PT is >=5%, as well as the number of these TEAEs by SOC and PT
- Number and percentage of patients experiencing at least one SAE (ocular or systemic together), as well as the number of these SAEs by SOC and PT

**Individual listings of AEs**

Listings of AEs (ocular and systemic separately) will be produced:

- for non-emergent AEs on enrolled patients,
- for TEAEs, serious TEAEs and TEAEs leading to premature IMD discontinuation.

The following variables will be presented:

- Patient number,
- Studied eye (right eye / left eye),
- Gender,
- Age at baseline (Day 1),
- Diagnosis (verbatim),
- SOC,
- PT,
- Localisation (right eye / left eye / both eyes),
- Date of onset,
- Time to occurrence (days) from the date of the first IMD instillation,
- Date of recovery / date of death, if any,
- Duration (days),
- Outcome,
- Details of AEs,
- Frequency and details (i.e. Did the AE appear upon IMD administration; If yes, mean duration of each episode),
- Severity,
- Seriousness,
- Relationship to IMD,
- Relationship to protocol procedure,
- Action taken with IMD,

- Required treatment,
- Required surgical/medical procedure.

Listings will be sorted by patient identifier and date of onset.

Listing of Deaths, Other Serious Adverse Events, Discontinuations due to AEs and Other AEs of Special Interest (if applicable) will be also provided for narratives (in word and excel files).

Discontinuations due to AEs include IMD-related AE leading to premature IMD discontinuation OR study withdrawal (*i.e.*, drug related AE with action taken = drug withdrawn OR End of study with premature discontinuation due to this AE).

#### 7.10.2 Device Deficiency

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#### 7.10.3 Far BCVA

Far BCVA in LogMar will be described at each assessment time (baseline, and D36) for the studied eye and the contralateral eye. Change from baseline at D36 will be described as well.

#### 7.10.4 Tolerance assessment

Ocular tolerance by the investigator assessed on a 4-point ordinal scale (Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory) will be presented at D15 and D36 by frequency distribution for each modality.

Ocular tolerance by the patient assessed on a 4-point ordinal scale (Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory) will be presented at D15 and D36 by frequency distribution for each modality.

# 8 Interim Analysis

Not Applicable

# 9 Changes from Study Protocol

Changes from protocol are the following:

- Description by classes has been added for the OSDI parameter,
- Definition of evaluable patients and FAS has been specified,
- Analysis on details of TEAEs has been reviewed.

# 10 References

[1] ISO 14155:2020 standard (clinical investigation of medical devices for human subjects - Good Clinical Practice)

[2] European Medical Device (MDR) Regulation 2017/745

[3] MDCG 2020-10/1 Rev 1: Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 October 2022