STATISTICAL ANALYSIS PLAN

Protocol: LT2769-001 / 17E1044

Efficacy and Safety Assessment of T2769 in patients with moderate to severe Dry Eye Syndrome

National, multicentre, open-label

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ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical
FBCVA	Far Best Corrected Visual Acuity
CI	Confidence Interval
CRF	Case Report Form
D	Days
DED	Dry Eye Disease
ICH	International Conference on Harmonisation
ITT	Intent-To-Treat
IP	Investigational Product
LOCF	Last Observation Carried Forward
MedDRA	Medicinal Dictionary for Regulatory Activities
mITT	modified Intent-To-Treat
OSDI	Ocular Surface Disease Index
PP	Per Protocol
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TBUT	Tear Break-up Time
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analog Scale
WHO-DD	World Health Organisation-Drug Dictionary

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses to be performed on the study, contains the definition of analysis sets, defines derived data, and specifies the methodology for analysing primary and secondary efficacy endpoints and safety endpoints.

This SAP is based on:

- Study Protocol final version 2.0 dated on 13-NOV-2017,
- Case Report Form (CRF) final version 1.0 dated on 06-DEC-2017,

The analyses closely follow the ICH guidelines for industry on topic E3 - Structure and Content of Clinical Study Reports and E9 - Statistical Principles for Clinical Trials.

Any changes from the planned analyses will be described and justified in the clinical study report.

1 DESCRIPTION OF THE STUDY

1.1 Study objectives

1.1.1 Primary objective

The primary objective is to assess the efficacy of T2769 in patients with moderate to severe Dry Eye Syndrome.

1.1.2 Secondary objective(s)

The secondary objective is to assess safety of T2769.

1.2 Study design

1.2.1 Description

This is a study in open, non-comparative, multicentre, on ambulatory patients.

1.2.2 Schedule of assessments and study procedures

All patients were expected to attend four visits during the course of the investigation as presented below:

- Visit#1: Screening visit Day -14/D-10.
- Visit#2: Day 1.
- Visit#3: Day 14 (+/- 1 day).
- Visit #4 - Final Visit: Day 42 (+/-5 days).

FLOW CHART: Study investigations were to be conducted as per the following schedule of study procedures:

Study procedure	Screening visit Visit# 1 D-14/D-10	Run-in Period	Inclusion visit Visit# 2 D1	Visit# 3 Day 14 (+/- 1 day)	Final Visit Visit# 4 Day 42 (+/- 5 days) Or withdrawal visit
Informed consent	X	Preservative free artificial tears (NaCl 0.9%)			
Demographic information	X				
Ocular and systemic medical and surgical history	X				
Previous and concomitant ocular and systemic treatments	X		X	X	X
History of Dry Eye	X				
Symptomatology evaluation (Visual Analog Scale [VAS])	X		X	X	X
Ocular symptoms	X		X	X	X
Ocular symptoms upon instillation				X	X
Soothing sensation within 15 min after IP instillation				X	X
Far Best Corrected Visual Acuity in both eyes	X				X
Ocular Surfiace Disease Index (OSDI) score			X	X	X
Schirmer test			X	X	X
Slit Lamp examination					
Tear Break up Time (TBUT)	X		X	X	X
Oxford 0-15 grading scheme Scale	X		X	X	X
Van Bijsterveld staining	X		X	X	X
Conjunctival hyperaemia (Mac Monnies photographic scale)	X		X	X	X
Auxiliary product dispensation	X				
Auxiliary product compliance			X		
Investigational product dispensation			X	X	
Investigational product compliance				X	X
Adverse events			X	X	X
Ocular efficacy assessment by the investigator				X	X
Ocular tolerance assessment by the investigator				X	X
Ocular tolerance assessment by the patient				X	X

1.3 Study endpoints

1.3.1 Primary efficacy endpoint

The primary efficacy endpoint is the evolution of the ocular symptomatology on a Visual Analog Scale (VAS) between D1 and after 42 days of treatment (D42).

1.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Evolution of global ocular staining score according to Oxford 0-15 grading scheme (fluorescein coloration) between Day 1 (D1) and after 42 days of treatment (Day 42 [D42]),
- Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and after 42 days of treatment (D42),
- Soothing sensation assessed by the patient at D42.

1.3.3 Other efficacy endpoints

1.3.3.1 Other evaluation parameters at D14

The other efficacy criteria at D14 are:

- Evolution of the ocular symptomatology on a VAS between D1 and after 14 days of treatment (D14),
- Evolution of global ocular staining according to Oxford 0-15 grading scheme (fluorescein coloration) between D1 and after 14 days of treatment (D14),
- Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and after 14 days of treatment (D14),
- Soothing sensation assessed by the patient at D14.

1.3.3.2 Other evaluation parameters at D14 and D42

The other efficacy criteria at D14 and D42 are:

- Evolution of Ocular Surface Disease Index (OSDI) score after 14 days (D14) and 42 days of treatment (D42).
- Evolution of the following Dry Eye symptoms after 14 days (D14) and 42 days of treatment (D42): burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, tearing, light sensitivity graded by the patient.
- Evolution of conjunctival hyperaemia at slit lamp examination after 14 days (D14) and 42 days of treatment (D42).
- Evolution of Schirmer test (without anaesthesia) after 14 days (D14) and 42 days of treatment (D42).
- Evolution of Tear Break-Up Time (TBUT) after 14 days (D14) and 42 days of treatment (D42).
- Ocular efficacy assessment by the investigator using a 4-point verbal scale at D14 and D42.

1.3.4 Safety endpoints

Safety assessment criteria are:

- Ocular symptoms upon instillation including burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, and other symptoms graded by the patient after 14 days and 42 days of treatment with the T2769
- Far best corrected visual acuity (FBCVA) after 42 days of treatment with the T2769,
- Ocular tolerance assessment by the investigator after 42 days of treatment with the T2769,
- Ocular tolerance assessment by the patient after 42 days of treatment with the T2769,

- Ocular and Systemic Adverse Events (AEs) recorded throughout the investigation by the investigator.

1.4 Study treatments

1.4.1 Treatment groups

Each patient was instructed to instill the IP T2769 for 42 days, one drop in each eye, 3 to 6 times daily.

1.4.2 Randomisation

1.4.2.1 Randomisation procedure

Not Applicable.

1.4.2.2 Masking

Not Applicable.

1.5 Sample size considerations

The primary efficacy criterion is the change from baseline in ocular symptoms at D42 assessed using a VAS. Assuming that the mean change is 12, the standard deviation (SD) is 23, the correlation between pairs is 0.4, a total of 50 evaluable patients achieves a power of at least 90% (calculated power = 91%) for the two-sided test for no difference with a normal distribution and a significance level of 5%.

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Number of Sides	2
Alpha	0.05
Mean Difference	-12
Standard Deviation	23
Correlation	0.4
Number of Pairs	50
Null Difference	0
Computed Power	0.910

A total of 55 patients should be enrolled in the study to take into account approximately 10% of non-evaluable patients. Estimates of the mean, SD and correlation between pairs are based upon data of previous studies (Laboratoires THEA. Clinical study LT2762-PIV-11/13, 2017) SAS 9.4 was used for the sample size calculation (POWER procedure, PAIRED MEANS statement).

2 ANALYSIS SETS

The following analysis sets will be considered.

2.1 Safety set

The Safety set will include all enrolled patients having received at least one dose of the IP. The Safety set will be the primary population for the safety analysis.

Note: Enrolled patients will be patients who have signed the informed consent and for whom the screening visit (D-10) has been recorded in the CRF.

2.2 Modified intent-to-treat set

The modified intent-to-treat (mITT) set will include all enrolled patients having received at least one dose of the IP and with at least one baseline and post-baseline efficacy assessment. mITT set will be the primary population for the efficacy analysis.

2.3 Per-protocol set

The Per-protocol (PP) set will include all mITT patients without any major violation of clinical investigational procedures. Deviations from the protocol including violations of inclusion/exclusion criteria will be detailed in a separate document and assessed as “minor” or “major” in cooperation with the sponsor during a blind review meeting prior to the database lock. PP set will be considered as a secondary population and will be used for sensitivity analyses.

3 GENERAL CONSIDERATIONS FOR DATA ANALYSES

Statistical analyses will be performed by the Biostatistics unit of AIXIAL. Analyses will be conducted with SAS® software, version 9.4 (SAS Institute, North Caroline, USA).

All tables will present the result for the overall population.

Quantitative variables (Continious data) will be summarized in summary tables indicating the number of non-missing observations (n), mean, SD, median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% Confidence Interval (CI) of the mean/median.

Qualitative variables (Categorical data) will be summarized in summary tables indicating 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 score method of Wilson without continuity correction:

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

With n = number of non-missing observations

p = percentage

q = 1 – p

z = 1.96 for two-sided 95%CI

Except 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).

Variables recorded for each eye will be described separately for the worse eye and for the other eye (if applicable).

An eye is eligible if it respects the inclusion criteria without exclusion criteria (ophtalmological criteria) at screening visit and inclusion visit.

The worse eye is defined as:

- For patients with both eligible eyes:
  - Eye with the worse Oxford score (higher value);
  - if same Oxford score in both eyes: eye with the worse Schirmer score (lower value);
  - if same Oxford and Schirmer scores in both eyes: eye with the worse TBUT score (lower value);
  - if same Oxford, Schirmer and TBUT scores in both eyes: right eye.
- For patients with one eligible eye: eligible eye.
- For patients with both not eligible eyes:
  - Eye with the worse Oxford score in the range ≥ 4 and ≤ 9;
  - if same Oxford score in both eyes: eye with the worse Schirmer score in the range ≥ 3 and ≤ 9 mm/5min;
  - if same Oxford and Schirmer scores in both eyes: eye with the worse TBUT ≤ 30 seconds;
  - if same Oxford, Schirmer and TBUT scores in both eyes: or no eye in the range for these 3 criteria right eye.

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

Quantitative parameters will be compared between visits using paired t-test. Assumptions underlying the Student test will be checked:

- Kolmogorov-Smirnov test will be performed to check the assumption of normality,
- Normal probability plot ≤ QQ-plot will be performed to check the assumption of normality,

If there is a strong violation of normality assumption, in addition to the initial model, a Signed rank test will be performed.

For centre effect, primary endpoint will be compared between centre using Analysis of Variance (ANOVA). Assumptions underlying the ANOVA for the sensitivity analyses will be checked:

- Kolmogorov-Smirnov test will be performed to check the assumption of normality,
- Normal probability plot and QQ-plot will be performed to check the assumption of normality,
- Levene's test will also be performed to check the homogeneity of variances.

If there is a strong violation of homogeneity of variances or normality assumption, in addition to the initial model, a Kruskal-Wallis test will be performed.

A document will be provided to summarize normality.

3.1 Display of analysis results

Following labelling will be used in statistical tables: "T2769" (single group) or "TUN001" / "TUN002" / "TUN003" and "Total" (by centre).

3.2 Interim analyses

No interim analysis will be performed.

3.3 Centre effect management

Centre effect will be tested by ANOVA for the primary endpoint (Section 6.1.3).

3.4 Subgroup analyses

The primary efficacy criterion and secondary criteria will be described by centre.

3.5 Other strata and covariates

Not Applicable.

3.6 Multiple comparisons and multiplicity

There is a single primary efficacy endpoint in the study (comparaison of symptomatology evaluation between D1 and D42). Other efficacy measures are defined to be of secondary importance. Thus comparison will be performed at a two-sided significance level of 0.05; no adjustment of the type I error rate will be made.

4 DATA HANDLING CONVENTIONS

4.1 Visit windows

All data will be recorded and organised according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit.

Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected after D1 can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: the closest non-missing result to the scheduled visit should be used.

Scheduled visit post baseline	**Time interval (days)**
Follow-up visit (D14+/-1)	1 to 27 days
Final visit (D42+/-5)	28 to 55 days
Time interval (days): Date of visit – Date of inclusion visit (D1)	

Moreover, last visits recorded more than 24h after the last instillation will not be considered in the analysis.

4.2 Premature discontinuation and missing data

If a patient is prematurely withdrawn from the study for any reason, the investigator must make every effort to perform the evaluations described for the D42 visit.

In the mITT set, missing values will be imputed using the last observation available on treatment method (LOCF).

4.3 Derived and transformed data

Following derived data used for analyses will be calculated.

4.3.1 Baseline

Baseline will be defined for each assessment as an evaluation before the first instillation of the IP.

- For FBCVA, value recorded at Screening visit will be the baseline
- For others parameters, value recorded at Day 1, will be the baseline

Baseline value will be the one in the concerned eye for endpoints assessed/analysed by eye.

4.3.2 Age (years)

Age (years) will be calculated in classes as: Age < 65 vs Age ≥ 65.

4.3.3 Time since Dry Eye Disease (DED) diagnosis

Time since Dry Eye Disease (DED) diagnosis (months) will be calculated as:
(Date of screening Visit [D-14/D-10] – 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 screening visit [D-14/D-10] – Year of diagnosis) x 12.

4.3.4 Duration of treatment

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

Duration of IP (days) will be calculated as (Date of last instillation at D42 or premature discontinuation visit – Date of first instillation at D1) + 1.

If the day or the month is missing for one of the dates, the duration of treatment (physiol or IP) will be missing.

4.3.5 Mean dose regimen (instillations / day)

The mean dose regimen (instillations / day) will be calculated in classes as:
Mean dose regimen ≤ 4 vs Mean dose regimen > 4.

4.3.6 Change from baseline

Change from baseline will be calculated as the difference:
Assessment at the visit – Assessment at baseline.

4.3.7 Change from baseline in classes

Change from baseline in classes will be defined as detailed below:

In four classes:

- Improvement (Decrease of score from baseline): Change from baseline < 0
- Absence stable: Change from baseline = 0 and absence of symptoms
- Presence stable: Change from baseline = 0 and presence of symptoms
- Worsening (Increase of score from baseline): Change from baseline > 0

In three classes compared to 0:

- Improvement (Decrease of score from baseline): Change from baseline < 0
- No change: Change from baseline = 0
- Worsening (Increase of score from baseline): Change from baseline > 0

In three classes compared to -1/1:

- Improvement of more than 1 point: Change from baseline < -1
- No change: Change from baseline ≥ -1 and ≤ 1
- Worsening of more than 1 point: Change from baseline > 1

4.3.8 Symptomatology evaluation (mm)

The Symptomatology evaluation (on VAS) will be calculated as follows:
[VAS Score (mm) / Scale length (mm) x 100].

4.3.9 Global ocular staining

The Global ocular staining assessed using a 15-point scale (grades of 0–5) will be calculated by adding the individual scores of the three zones (Temporal bulbar conjunctiva, corneal area, nasal bulbar conjunctiva). If any individual score is missing, so will be the global score.

4.3.10 Van Bijsterveld score

The corneo-conjunctival exposed surface is separated in three parts: nasal bulbar conjunctive, corneal area, and temporal bulbar conjunctive. The following score will be attributed to each of these parts with the help of a visual figure representing each degree of staining:

(0) = No coloration
(1) = Some punctuations.
(2) = Well defined punctuations.
(3) = Total coloration.

The Van Bijsterveld score is the addition of the scores obtained in the three parts (nasal, corneal and temporal). If any individual score is missing, so will be the Van Bijsterveld score.

4.3.11 Ocular Surface Disease Index (OSDI)

The OSDI score will be calculated as follows:
[(Sum of the scores for all questions answered x 25] / [(total number of questions answered)].

The OSDI score will be also calculated in classes:

- None: ≥0 and <13; Mild: ≥13 and <23; Moderate: ≥23 and <33; Severe: ≥33 and ≤ 100;
- <18 vs ≥18.

4.3.12 Total score of ocular symtoms

The following dry eye symptoms have been assessed for both eyes (globally) and collected using a 4-point ordinal scale (0 = absent to 3 = severe, very distressing and interfering with daily activities):

- burning/irritation,
- stinging/eye pain,
- ichting/pruritus,
- eye dryness feeling,
- foreign body sensation,
- tearing,
- light sensitivity.

The total score of ocular symtoms (ranging from 0 to 21) will be calculated by adding the individual scores of the seven symptom scores, higher score representing greater distress. If any symptom is missing, so will be the total score.

4.3.13 Schirmer score

Schirmer score will be calculated in classes as:
<5, ≥5 and <10 and ≥10 mm/5 minutes.

4.3.14 Tear Break-Up Time (TBUT)

TBUT mean (seconds) will be calculated as:
Mean of (1st measure, 2nd measure, 3rd measure).

If only one measure is recorded, this single measure will be used for assessment of the mean.

The TBUT score will be also derived in classes: <5, ≥5 and ≤10 and >10 seconds.

4.3.15 Ocular symptoms upon instillation

Duration of ocular symptoms upon instillation:
If seconds are missing and minutes are present, the seconds are 0.
If minutes is missing and hours are present, the minutes and seconds are 0.

Total score of ocular symptoms upon instillation:
The total score of ocular symptoms upon instillation (ranging from 0 to 15) will be calculated by adding the individual scores of the five symptoms scores: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation. If any individual score is missing, so will be the total score.

4.3.16 Far Best Corrected Visual Acuity (FBCVA)

FBCVA will be calculated in Log Mar as: Log_{10} (10/ Visual acuity).

4.3.17 Adverse event (AE) time to occurrence

Time to AE occurrence (days) will be calculated as follows:
Date of onset – Date of IP first instillation.

4.3.18 AE duration

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

5 DESCRIPTION OF THE STUDY POPULATION

5.1 Disposition of patients

The number of enrolled patients will be presented. The number (%) of patients included in each analysis set (Safety, mITT and PP sets) will be presented. The number (%) of patients by centre will be presented for each analysis set.

The number (%) of patients per visit as considered in the analysis will be described on the Safety set, on the mITT set and for the PP set.

The number (%) of patients who prematurely discontinued the study and the primary reason for discontinuation will be presented on the Safety set and on the mITT set. A listing will be performed presenting the patients who prematurely discontinued the study with the detailed reason for discontinuation.

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 on the mITT set. The reasons for deviation will be also described on the mITT sets and an individual patient data listing with all minor/major deviations will be provided.

A listing of all the patients including information about populations and reason for exclusion, worse eye, will be performed on the enrolled patients' population.

A listing of of visits as considered in the analysis will be performed on the enrolled patient's population.

5.2 Demographics and baseline characteristics

The demographics and baseline characteristics of the patients will be described by centre on the mITT set and on the Safety set.

The following characteristics will be summarised:

- Demographic characteristics:
  - Age (years) as continuous and in classes (<65, ≥65 years old),
  - Gender,
  - Gender by age class (<65, ≥65 years old),
- Medical history (*)
  - Ocular medical and surgical history other than the studied disease.
  - Systemic medical history.
- Surgical history (*)
  - Ocular surgical history related to another disease than DED.
  - Systemic surgical history.

(*) Diagnoses (for medical history) and surgical procedures (for surgical history) will be coded using the Medicinal Dictionary for Regulatory Activities (MedDRA) version 21.1, September 2018 (English).

- Number (%) of patients will be presented by System Organ Class (SOC) and Preferred Term (PT). Ocular treatments (**)
  - Previous ocular treatments,
  - Concomitant ocular treatments.
- Non-ocular treatments (**)
  - Previous non-ocular treatments,
  - Concomitant non-ocular treatments.

(**) All previous and concomitant ocular and non-ocular treatments will be coded using the World Health Organisation-Drug Dictionary (WHO-DD Format C March 2017).

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

- History of Dry eye,
  - Localisation (Right / Left / Both),
  - Time since DED diagnosis (months),
  - Known Dry eye requiring artificial tears within the last three months (Yes / No),
  - Origin of Dry eye (Primary Sjögren syndrome / Secondary Sjögren syndrome / Meibomian gland deficiency / Non Sjögren aqueous deficiency / Other).

Data regarding contraception status will be presented in an individual data listing.

Values before first IP intake of the efficacy and safety endpoints will be provided in statistical tables with assessments at Visit 3 (D14) and Visit 4 (D42) (see Section 6).

5.3 Treatment exposure and compliance

The following data on the use of Physiol and IP will be summarised on the Safety and mITT sets:

- Physiol: duration of physiol (days),
- Treated eye(s) by IP (Right / Left / Both),
- Duration of IP (days),
- IP Mean daily dose regimen at Visit 3 (D14) and Visit 4 (D42) and in classes.

6 EFFICACY ANALYSIS

Primary efficacy endpoint will be primarily analysed on the mITT set. Sensitivity analyses will be also performed on the PP set. Secondary efficacy endpoints will be analysed on the mITT set and on the PP set, if difference of number of patients between PP and mITT sets is more than 10%.

6.1 Primary efficacy endpoint

The primary efficacy criterion is the change in ocular symptomatology assessed on a VAS between D1 and D42.

Descriptive statistics will be performed at each assessment time (Screening, Baseline, D14 and D42) overall and by centre. Change from baseline will be described as well.

6.1.1 Main analysis of the primary efficacy endpoint

To assess the efficacy of T2769, on change in ocular symptomatology assessed on a VAS between D1 and D42, estimate of the change and associated 95% CI will be provided, as well as p-value for the paired t-test on the mITT set. Based on the LOCF method, missing values will be replaced by the last available value.

The syntax with SAS using the UNIVARIATE procedure is detailed in APPENDIX 1.

6.1.2 Sensitivity analysis of the primary efficacy endpoint

Sensitivity analysis will be performed without replacement of missing values on the mITT and PP sets.

6.1.3 Secondary analysis on the primary efficacy endpoint

Secondary analysis will be performed on the primary efficacy endpoint to test centre effect. The change from baseline at D42 will be analysed using an ANOVA including centre as covariable. The adjusted mean by centre and their corresponding 95% CI will be estimated in this model.

This analysis will be performed based on the LOCF method on the mITT set and on the observed data on the PP set.

The syntax with SAS using the MIXED procedure is detailed in APPENDIX 1.

6.2 Secondary efficacy endpoints

Secondary performance endpoints will be analysed based on the LOCF method on the mITT set and on the observed data on the PP set (if difference of number of patients between PP and mITT sets is more than 10%).

6.2.1 Global ocular staining at D42

The Oxford 0-5 grading scheme assesses the staining in three zones: temporal bulbar conjunctiva, corneal area and nasal bulbar conjunctiva.

The score of each zone (ranging from 0 to 5) will be described at each assessment time (Screening, Baseline, D14 and D42) by worse eye and the contralateral eye separately, by frequency distribution.

Global ocular staining will be also described at each assessment time (Screening, Baseline, D14 and D42) by worse and contralateral eye separately. Change from baseline will be described as well.

Evolution of Global ocular staining will be analysed using paired t-test between D1 and D42 as for symptomatology assessment on the VAS at D42 (see Section 6.1.1) by worse and contralateral eye separately.

6.2.2 Van Bijsterveld score at D42

The corneo-conjunctival exposed surface is separated in three parts: nasal bulbar conjunctive, corneal area, and temporal bulbar conjunctive.

The score of each part (ranging from 0 to 3) will be described at each assessment time (Screening, Baseline, D14 and D42) by worse eye and the contralateral eye separately, by frequency distribution.

Van Bijsterveld score will be described at each assessment time (Screening, Baseline, D14 and D42) by worse and contralateral eye separately. Change from baseline will be described as well.

Evolution of Van Bijsterveld score will be analysed using paired t-test between D1 and D42 as for symptomatology assessment on the VAS at D42 (see Section 6.1.1), by worse and contralateral eye separately.

6.2.3 Soothing sensation at D42

The soothing sensation (None / Mild / Moderate / Important) will be assessed in global for both eyes at D42.

6.3 Other efficacy endpoints

Other endpoints will be analysed based on the LOCF method on the mITT set and on the observed data one the PP set (if difference of number of patients between PP and mITT sets is more than 10%).

6.3.1 Symptomatology evaluation at D14

Evolution of the ocular symptomatology will be analysed using paired t-test between D1 and D14 as for symptomatology assessment at D42 (see Section 6.1.1).

6.3.2 Global ocular staining at D14

Evolution of Global ocular staining will be analysed using paired t-test between D1 and D14 as for symptomatology assessment at D42 (see Section 6.1.1) by worse and contralateral eye separately.

6.3.3 Van Bijsterveld score at D14

Evolution of will be analysed using paired t-test between D1 and D14 as for symptomatology assessment at D42 (see Section 6.1.1) by worse and contralateral eye separately.

6.3.4 Soothing sensation at D14

The soothing sensation (None / Mild / Moderate / Important) will be assessed in global for both eyes at D14.

6.3.5 OSDI score

The OSDI score, ranging from 1 to 100 will be described at each assessment time (Baseline, D14 and D42). Frequency distribution of OSDI score (none, mild, moderate, severe then <18 , ≥18) will be also presented at each assessment time (Baseline, D14 and D42).

Evolution of OSDI score will be analysed using paired t-test between D1 and D14 and between D1 and D42 as for symptomatology assessment on the VAS at D42 (see Section 6.1.1).

6.3.6 Ocular symptoms

Ocular symptoms (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, tearing, light sensitivity) are assessed using a 4-point ordinal scale from 0 to 3, 0 indicating no symptom and 3 indicating very disturbing symptoms.

Frequency distribution of each symptom will be presented at each assessment time (Screening, Baseline, D14 and D42). In addition, frequency distribution of change from baseline in classes will be presented for each symptom at D14 and D42. Following categories will be defined: i) improvement (i.e. decrease of symptom score from baseline), absence stable, presence stable, worsening (i.e. increase of symptom score from baseline), ii) improvement, no change, worsening.

The total score of the seven symptoms, ranging from 0 to 21, will be calculated and presented for Screening, Baseline, D14 and D42. Change in total score from baseline will be also described D14 and D42.

Evolution of total score will be analysed using paired t-test between D1 and D14 and between D1 and D42 as for symptomatology assessment at D42 (see Section 6.1.1).

Data relative to other symptoms will be provided in an individual patient data listing. Other symptoms will be coded using MedDRA 21.1, September 2018 (English).

6.3.7 Conjunctival hyperaemia

Conjunctival hyperaemia will be assessed using the McMonnies photographic 6-point ordinal scale from 0 to 5. Frequency distribution will be presented at each assessment time (Screening, Baseline, D14 and D42), by worse and contralateral eye separately.

In addition, frequency distribution of change from baseline in classes will be presented for conjunctival hyperaemia at D14 and D42 on the worse eye and the contralateral eye. Following categories will be defined: i) improvement (i.e. decrease of symptom score from baseline), absence stable, presence stable, worsening (i.e. increase of symptom score from baseline), ii) improvement, no change, worsening, iii) improvement of more than 1 point (i.e. change from baseline < -1, no significant change (i.e. change from baseline ≥ -1 and ≤ 1), worsening of more than 1 point (i.e. change from baseline > 1).

6.3.8 Schirmer test

The Schirmer test will be described at each assessment time (Baseline, D14 and D42) by worse and contralateral eye separately. Frequency distribution of Schirmer test in classes (<5, ≥5 and <10, ≥10 mm/5 minutes) will be also presented at each assessment time (Baseline, D14 and D42).

Evolution of schirmer test will be analysed using paired t-test between D1 and D14 and between D1 and D42 as for symptomatology assessment at D42 (see Section 6.1.1), by worse and contralateral eye separately.

6.3.9 TBUT

TBUT mean will be described at each assessment time (Screening, Baseline, D14 and D42) by worse and contralateral eye separately. Frequency distribution of TBUT in classes (<5, ≥5 and ≤10,>10 seconds) will be also presented at each assessment time (Baseline, D14 and D42).

Evolution of TBUT mean will be analysed using paired t-test between D1 and D14 and between D1 and D42 as for symptomatology assessment at D42 (see Section 6.1.1), by worse and contralateral eye separately.

6.3.10 Ocular efficacy assessment by the investigator

Global judgment of efficacy by investigator assessed on a 4-point ordinal scale (Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory) will be presented by frequency distribution for each modality and frequency distribution after regrouping ‘very satisfactory’ with ‘satisfactory’, and ‘not very satisfactory’ with ‘unsatisfactory’, at D14 and D42.

7 SAFETY ANALYSIS

Safety endpoints will be analysed on the Safety set.

7.1 Ocular symptoms upon instillation

Ocular symptoms upon instillation (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation) are assessed using a 4-point ordinal scale from 0 to 3, 0 indicating no symptom and 3 indicating very disturbing symptoms.

Frequency distribution of each symptom will be presented at each assessment time (D14 and D42).

The duration (minutes) and the frequency will be described by symptom on the subgroup of patients presenting with the symptom (i.e. with severity ≥ 1).

The total score of the five symptoms, ranging from 0 to 15, will be calculated and presented for D14 and D42.

Data relative to other symptoms will be provided in an individual patient data listing. Other symptoms will be coded using MedDRA 21.1, September 2018 (English).

7.2 FBCVA

FBCVA will be summarised at screening visit and D42 using usual descriptive statistics for continuous variable, in Log Mar. Frequency distribution in classes (i.e., values from 1/10 to 10/10 and > 10/10, with non-integer numbers rounded to the nearest integer) will be also presented.

FBCVA will be presented by worse and contralateral eye separately.

7.3 Ocular tolerance assessment by the investigator

Ocular tolerance by the investigator assessed on a 4-point ordinal scale (Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory) will be presented by frequency distribution for each modality and frequency distribution after regrouping ‘very satisfactory’ with ‘satisfactory’, and ‘not very satisfactory’ with ‘unsatisfactory’.

Ocular tolerance assessment will be described at each assessment time (D14 and D42).

7.4 Ocular tolerance assessment by the patient

Ocular tolerance by the patient assessed on a 4-point ordinal scale will be presented by frequency distribution for each modality and frequency distribution after regrouping ‘very satisfactory’ with ‘satisfactory’, and ‘not very satisfactory’ with ‘unsatisfactory’.

Ocular efficacy assessment will be described at each assessment time (D14 and D42).

7.5 Ocular and systemic adverse events

Ocular and systemic AEs reported during the investigation will be coded with MedDRA 21.1, September 2018 (English).Ocular and systemic AEs will be analysed separately on the basis of the localisation as recorded by the investigator in the CRF.

Summary tables will be performed on treatment-emergent AEs (TEAEs). Non TEAEs will be described in individual patient data listings. TEAEs are AEs that occurred the same day or after the first IP administered. AEs that occurred the day of the first IP administered will be reviewed during a blind review meeting to decide if they have to be considered as TEAE or not.

7.5.1 Summary of adverse events

Separate summaries of treatment-emergent ocular and systemic AEs will be performed presenting the number and percentages of patients experiencing at least one:

- AE,
- Serious AE (SAE),

- Drug-related AE (i.e. related or missing relationship with the IP),
- Drug-related SAE (i.e. related or missing relationship with the IP),
- AE leading to premature study withdrawal.

7.5.2 Details of adverse events

Separately for ocular and systemic AEs, following descriptions will be performed:

- Number and percentage of patients experiencing at least one TEAEs as well as the number of TEAEs by SOC and PT. The same summary table will be performed for SAEs, drug-related AEs, drug-related SAEs and AEs leading to premature treatment withdrawal,
- Number and percentage of patients experiencing at least one TEAEs as well as the number of TEAEs by SOC, PT and severity,
- Number and percentage of patients experiencing at least one TEAEs as well as the number of TEAEs by SOC, PT and relationship with IP.

7.5.3 Individual listing of adverse events

Individual patient data listings of AEs will be performed for AEs, SAEs and drug-related SAEs, separately for ocular and systemic AEs. The following variables will be presented:

- Patient’s identifier,
- Gender,
- Age at baseline,
- Investigator's reported term,
- SOC,
- PT,
- Localisation,
- Date / Time of onset,
- Time to onset (days) from the date of the first IP instillation,
- Treatment-emergence,
- Date/Time of recovery / Date of death, if any,
- Duration (days),
- Outcome,
- Frequency and details,
- Severity,
- Action taken regarding the IP,
- Requirement for therapy adjustment/modification,
- Requirement for surgical / medical procedure and details,
- Seriousness,
- Relationship with the IP in the investigator’s opinion and details,
- Relationship with protocol procedure and details.

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

8 CHANGES FROM PROTOCOL

Changes from protocol are the following:

- The secondary efficacy endpoint “Evolution of Soothing sensation assessed by the patient between D1 and after 42 days of treatment (D42)” and the other efficacy endpoint “Evolution of Soothing sensation assessed by the patient between D1 and after 14 days of treatment (D14) have been replaced by “Soothing sensation assessed by the patient at D42” and by “Soothing sensation assessed by the patient at D14” as this parameter is not recorded at D1. Therefore no evolution analysis is possible (See Sections 1.3.2 and 1.3.3.1);
- ITT set has been deleted as the study is not randomised;
- Sensitivity analysis without replacement of missing values has been added for mITT set on the primary endpoint;
- Analysis of centre effect;
- Secondary efficacy endpoints will be analysed on the PP set if difference of number of patients between PP and mITT sets is more than 10%;
- Description by classes has been added for the following parameters: Mean dose regimen, OSDI, Schirmer test and TBUT Mean);
- Total score for ocular symptoms and Total score for ocular symptoms upon instillation have been added.

9 VALIDATION OF STATISTICAL PROGRAMMING

Validation of statistical programming will be performed in agreement with Aixial SOP.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings.

Double programming of worse/contralateral eye, derivation and analyses regarding primary endpoint will be performed by the lead statistician. Else, a third party will review all statistical outputs (tables, figures) and results from statistical tests/models, as well as SAS code of all statistical programs. This includes programs used to derive data and macros developed for the study.

Any undocumented updating of study data in statistical programs instead of change in clinical database (or source data) is not allowed. Specifically, this refers to the cases where subjects or the data are added/changed using a statistical program rather than updating the database. This kind of hard coding is usually proposed to correct deficiencies (missing values, wrong values, and wrong measurement units) in the database when these errors are detected after database lock.

No hard coding is done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after database lock (i.e. clinical study reports, publications, abstracts, etc.). For particular cases, a footnote will be added in the corresponding table.

This policy ensures integrity of clinical data, since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial database.

10 REFERENCES

[1] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

APPENDIX 1. SAS SYNTAX FOR STATISTICAL MODELS PROGRAMMING

Main analysis of the primary efficacy endpoint (Section 6.1.1)

The syntax with SAS using the univariate procedure for each assessment time (D14 and D42) will be:

```
Proc univariate data=;
        Var Var;
Run;
```

Secondary analysis on the primary efficacy endpoint (Section 6.1.3)

The syntax with SAS using the mixed procedure will be:

```
Proc MIXED data=…;
      Class Centre;
      Model Change = Centre;
      LSMeans Centre / CL;
Run;
```

In case of strong violation, Kruskal Wallis test will be performed. The syntax with SAS using the npar1way procedure for each centre will be:

```
Proc NPAR1WAY data=… WILCOXON;
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Run;
```

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Table 4.122 Analysis of Schirmer test (mm/5min) – Change from baseline at D14 and D42 – Student – Observed data – Contralateral Eye – PP set
Table 4.123 Summary of Mean TBUT (seconds) – Worse Eye – PP set
Table 4.124 Summary of Mean TBUT (seconds) and Change from baseline – Worse Eye – PP set
Table 4.125 Analysis of Mean TBUT (seconds) – Change from baseline at D14 and D42 – Student – Observed data – Worse Eye – PP set
Table 4.126 Summary of Mean TBUT (seconds) – Contralateral Eye – PP set

Table 4.127 Summary of Mean TBUT (seconds) and Change from baseline – Contralateral Eye – PP set
Table 4.128 Analysis of Mean TBUT (seconds) – Change from baseline at D14 and D42 – Student – Observed data – Contralateral Eye – PP set
Table 4.1129 Ocular efficacy assessment by the investigator – PP set

5. Safety analysis

Table 5.1 Summary of Ocular symptoms upon instillation– Burning/Irritation – Safety set
Table 5.2 Summary of Ocular symptoms upon instillation – Stinging/Eye pain – Safety set
Table 5.3 Summary of Ocular symptoms upon instillation – Itching/Pruritus – Safety set
Table 5.4 Summary of Ocular symptoms upon instillation – Eye dryness feeling – Safety set
Table 5.5 Summary of Ocular symptoms upon instillation – Foreign body sensation – Safety set
Table 5.6 Summary of Total score of ocular symptoms upon instillation – Safety set
Listing 5.1 Listing of data relative to other ocular symptoms upon instillation – Safety set
Table 5.7 Summary of FBCVA – Worse eye – Safety set
Table 5.8 Summary of FBCVA – Contralateral eye – Safety set
Table 5.9 Ocular tolerance assessment by the investigator – Safety set
Table 5.10 Ocular tolerance assessment by the patient – Safety set
Table 5.11 Overview of treatment-emergent ocular adverse events – Safety set
Table 5.12 Summary of treatment-emergent ocular AEs per SOC and PT – Safety set
Table 5.13 Summary of treatment-emergent ocular SAEs per SOC and PT – Safety set
Table 5.14 Summary of treatment-emergent ocular drug-related AEs per SOC and PT– Safety set
Table 5.15 Summary of treatment-emergent ocular drug-related SAEs per SOC and PT – Safety set
Table 5.16 Summary of treatment-emergent ocular AEs leading to premature withdrawal per SOC and PT – Safety set
Table 5.17 Summary of treatment-emergent ocular AEs per SOC, PT and severity – Safety set
Table 5.18 Summary of treatment-emergent ocular AEs per SOC, PT and relationship to the IP – Safety set
Table 5.19 Overview of treatment-emergent systemic adverse events – Safety set
Table 5.20 Summary of treatment-emergent systemic AEs per SOC and PT – Safety set
Table 5.21 Summary of treatment-emergent systemic SAEs per SOC and PT – Safety set
Table 5.22 Summary of treatment-emergent systemic drug-related AEs per SOC and PT– Safety set
Table 5.23 Summary of treatment-emergent systemic drug-related SAEs per SOC and PT – Safety set
Table 5.24 Summary of treatment-emergent systemic AEs leading to premature withdrawal per SOC and PT – Safety set
Table 5.25 Summary of treatment-emergent systemic AEs per SOC, PT and severity – Safety set
Table 5.26 Summary of treatment-emergent systemic AEs per SOC, PT and relationship to the IP – Safety set

APPENDIX 3. EXEMPLE OF TABLES

Study: LT2769-001 Page X / N
Population: xxx set

Table x – Summary of qualitative and quantitative variable

	TUN001 (N=XX)	TUN002 (N=XX)	TUN003 (N=XX)	TOTAL (N=XX)
Quantitative variable				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
95% CI (mean)	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]
Median	xx.x	xx.x	xx.x	xx.x
Q1 ; Q3	xx.x	xx.x	xx.x	xx.x
Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx
Missing data	xx	xx	xx	xx
Qualitatite variable				
n	xx	xx	xx	xx
Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
95% CI (Modality 1)	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]
Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
95% CI (Modality 2)	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]	[xx.x%;xx.x%]
…				
Missing data	xx	xx	xx	xx

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Study: LT2769-001 Page X / N
Population: xxx set

Table x – Summary of quantitative variables and Change from baseline

				Parameter at each visit					Change from Baseline				
Variable	Centre	N	Visit	n	Mean (SD)	Median	Min ; Max	95% CI (Mean)	n	Mean (SD)	Median	Min ; Max	95% CI (Mean)
	TUN001	XX	Screening	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			Baseline	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			D14	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42 - LOCF	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
	TUN002	XX	Screening	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			Baseline	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			D14	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42 - LOCF	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
	TUN003	XX	Screening	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			Baseline	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			D14	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42 - LOCF	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
	TOTAL	XX	Screening	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			Baseline	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]					
			D14	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]
			D42 - LOCF	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]	XX	XX.X (X.X)	XX.X	XX ; XX	[XX.X;XX.X]

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Study: LT2769-001 Page X / N
Population: xxx set

Table x – Analysis of quantitative variable – Change from baseline – Student

	T2769 (N=XX)
Change from baseline at Dx	
n	xx
Mean (SD)	xx.x (xx.x)
95% CI (Mean)	[xx.x;xx.x]
Median	xx.x
Min. ; Max.	xx ; xx
p-value	x.xxx (T)
Missing data	xx
(T) Student's t test or (RS) Rank signed test	

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Study: LT2769-001 Page X / N
Population: xxx set

Table x – Analysis of centre effect – ANOVA

	TUN001 (N=XX)	TUN002 (N=XX)	TUN003 (N=XX)
Number of patients in the model	xx	xx	xx
Change from baseline at D42			
Adjusted mean (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
95% CI of Adjusted mean	[xx.xx; xx,xx]	[xx.xx; xx,xx]	[xx.xx; xx,xx]
Centre effect	0.xxx		

Note: p-value of Kruskal Wallis will be presented only in case of strong violation of ANOVA models

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Study: LT2769-001 Page X / N
Population: xxx set

Table x – Analysis of centre effect – Kruskal Wallis

	TUN001 (N=XX)	TUN002 (N=XX)	TUN003 (N=XX)
Number of patients in the model	xx	xx	xx
Centre effect	0.xxx		

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Date and time program was run: JJMMMYYYY HH:MM

Study: LT2769-001 Page X / N
Population: xxx set

Table x – Summary of AEs per SOC and PT

	T2769 (N=XX)	
	Nb of AEs	Nb (%) of patients
At least one (*)	xx	x (xx.x%)
Body system 1	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)
…		
Preferred term n	xx	xx (xx.x%)
Body system 2	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)
…		
Preferred term n	xx	xx (xx.x%)
….		
Body system n	xx	xx (xx.x%)
Preferred term 1	xx	xx (xx.x%)
Preferred term 2	xx	xx (xx.x%)
…		
Preferred term n	xx	xx (xx.x%)

Nb of AEs: Number of adverse events – Each AE is counted once per System Organ Class / Preferred Term
Nb (%) of patients: Number (%) of patients with at least one AE - Each patient is counted once per Preferred Term then per System Organ Class

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