Groupe Axonal-Biostatem
Parc d'activités Via Domitia
205, avenue des Gardians
34160 CASTRIES - FRANCE
☎: 33 (0) 4 67 04 87 54
🖷: 33 (0) 4 67 04 87 71
E-mail: contact@biostatem.com

Sponsor

Laboratoires THÉA
Research and Development Department
12, rue Louis Blériot
63017 Clermont-Ferrand Cedex 2, France

STATISTICAL ANALYSIS PLAN

Comparison of the performance and safety of T2259 versus Vismed® Multi in dry eye patients with superficial keratitis.

Investigation No. LT2259-001

Ref Axonal-Biostatem: E876

Type of study:	Investigation (Medical device)
Statistician:	[redacted]
Version number:	**No. 1.2**
Date of issue:	01JUL2021
Type of report:	Final

HISTORY OF THE VERSIONS

Version	Concerned parts	Date	Nature(*)	Reasons of change
Draft 0.1	All	03SEP2020	C	
Draft 0.2	All	27JAN2021	M	Review of the sponsor
Draft 0.3	All	28APR2021	M	Review of the sponsor
Draft 0.4	All	10JUN2021	M	Review of the sponsor
Final 1.0	All	16JUN2021	M	Review of the sponsor
Final 1.1	All	29JUN2021	M	Review of MW and biostatistician
Final 1.2	All	01JUL2021	M	Review of sponsor for consistency

(*) C: Creation, M: Modification, A: Addition, D: Delete

SIGNATURE FORM

Author of the Statistical Analysis Plan: [redacted] (statistician, Axonal-Biostatem)

Date:

Signature:

Proofreading and validation by Axonal-Biostatem:

[redacted]

TABLES OF CONTENTS

LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
AE	Adverse Events
ADE	Adverse Device Effect
ATC	Anatomical Therapeutic Chemical Classification
ANCOVA	Analysis of Covariance
AUF	Arbitrary Units of Fluorescence
BCVA	Far Best-corrected visual acuity
BR	Blind Review
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID	Corona Virus Disease
CSR	Clinical Study Report
D1, D8, D35, D84	Day 1/8/35/84
DEQ-5	Dry Eye Questionnaire – 5
e-CRF	Electronic Case Report Form
CRO	Contract Research Organisation
FAS	Full Analysis Set
FPFV	First Patient First Visit
FPLV	First Patient Last Visit
HLA-DR	Human Leukocyte Antigen – antigen D Related
ICH	International Conference of Harmonisation
IMD	Investigational Medical Device
IWRS	Interactive Response System
LOCF	Last Observation Carried Forward
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LS	Least Square
MD	Medical Device
MedDRA	Medical Dictionary for Regulatory Activities
Min.; Max.	Minimum; Maximum
MMRM	Mixed Model for Repeated Measures
OSI	Optical Scattering Index
OSDI	Ocular Surface Disease Index
OQAS	Optical Quality Analysing System
PP	Per Protocol
PT	Preferred Term
Q1; Q3	First Quartile; Third Quartile
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

SAF	Safety (population)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TBUT	Tear Break-up Time
TEAE	Treatment emergent adverse events
WHO	World Health Organisation

The Statistical analysis Plan (SAP) aims to describe the statistical analyses that will be performed for the study **LT2259-001**, based on the study protocol (Version 3.0 – 3 January 2020) and the e-Case Report Form (e-CRF) (Version MSC003, dated on 06 APR 2020), in accordance with ICH Guidelines and the general statistical principles.

This document is written by the AXONAL-BIOSTATEM statistician and reviewed and approved by the Sponsor of the Investigation (Laboratoires Théa) before the database lock.

1 STUDY OBJECTIVES

1.1 Primary objective

The primary objective of this study is to demonstrate the non-inferiority of T2259 versus Vismed® Multi in terms of performance.

Non-inferiority will be tested by calculating the bilateral 95% CI of the difference between groups (T2259 – Vismed® Multi) of the change from baseline of total ocular staining according to Oxford 0-15 grading scheme on Day 35. If the upper bound is no higher than 2 points, it will be concluded that the null hypothesis can be rejected and that the performance of T2259 is non-inferior to that of Vismed® Multi.

The non-inferiority analysis will be provided primarily in the PP population and confirmed in the FAS population.

1.2 Secondary objective

The secondary objective of the investigation is to evaluate the safety and the performance of T2259 versus Vismed® Multi.

2 STUDY DESIGN

2.1 Overview

This is a multicentre, randomised study, investigator-masked, 2 parallel groups (T2259 versus Vismed® Multi) of 38 evaluable patients each.

The patients were randomised after a run-in-period of 7 to 10 days with preservative free artificial tears (Hydrabak®, one drop in each eye 3 to 6 times daily). Then, they were treated with either T2259 or the reference product (Vismed® Multi) for 84 days (± 7 days).

Investigation visits were performed as following:

Day 1-10/Day 1-7	Selection visit (Visit 1)
Day 1	Randomisation/ Inclusion visit (Visit 2)
Day 8 (± 1)	Visit 3 Optional Visit (if the investigator and/or the patient thinks it is necessary)
Day 35 (± 3)	Visit 4
Day 84 (± 7)	Final visit (Visit 5)

The Visits V2, V3, V4 and V5 should have been performed at the same hour (±4 hours).

Reclassification of visits:

All "premature withdrawal" visits will be reclassified as decided in BR Meeting. Number of days between premature withdrawal visits and randomisation visit will be calculated and depending of this number of days, visits will be reclassified to the nearest planned non-missing visit.

2.2 Study population

2.2.1 Inclusion criteria

At selection visit (Day 1-10/Day 1-7):

- Informed consent signed and dated.
- Male or female aged ≥ 18 years old.
- Known Dry Eye Syndrome requiring artificial tears within the last 3 months prior to study selection.

At randomisation visit (Day 1):

- Patient having used only unpreserved artificial tears (Hydrabak®) as ocular medication during the run-in period (from Day 1-10/Day 1 -7 to Day 1).
- No ocular instillation at least 6 hours prior to the randomisation visit (Day 1).
- Diagnosis of moderate to severe dry eye syndrome defined by OSDI Score ≥ 23.
- Patients having at least one Eligible Eye, defined by both following conditions:
    - Total ocular staining (corneal and conjunctival) with Oxford 0- 15 grading scheme ≥ 4 and ≤ 9.

  AND

    - At least one of the following objective signs:
        - Schirmer test ≥ 3 mm/5 min and ≤ 9 mm/5 min Or
        - TBUT: sum of 3 measurements ≤ 30 seconds.

2.2.2 Exclusion criteria

Ophthalmic Exclusion Criteria in AT LEAST ONE EYE:

- Far best-corrected visual acuity ≤ 2/10.
- Severe blepharitis (grade 3 / 0-3 scale).
- Ocular rosacea.
- Severe Dry Eye associated to:
    - Eyelid malposition,
    - Corneal dystrophy,
    - Ocular neoplasia,

  - Filamentous keratitis,
  - Corneal neovascularisation,
  - Orbital radiotherapy.
- History of ocular trauma, ocular infection or ocular inflammation within the last 3 months.
- History of ocular allergy.
- History of uveitis.
- History of inflammatory corneal ulcer within the last 12 months.
- Glaucoma, ocular hypertension requiring glaucoma treatment.

Systemic/Non-Ophthalmic Exclusion Criteria:

- Known or suspected hypersensitivity to one of the components of the Investigational Device or auxiliary products.
- History of active relevant systemic condition incompatible with the study or likely to interfere with the study results or the patient safety according to investigator judgment.
- Allergic rhinitis active or susceptible to reactivate during the study.
- Any other medical or surgical history, disorder or disease susceptible to require or to modify systemic medication during the study (systemic medication having to be stable within the three months before selection).

Specific Exclusion Criteria Regarding Childbearing Potential Women:

- Pregnancy or breastfeeding.
- Childbearing potential woman who is not using a reliable method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant, vaginal ring, patch) and is not surgically sterilised.

Exclusion Criteria Related to General Conditions

- Inability of patient to understand the study procedures or to give informed consent.
- Non-compliant patient (*e.g.*, not willing to attend a visit or completing the self-questionnaire; way of life interfering with compliance).
- Participation in this investigation at the same time as another clinical investigation.
- Participation in this investigation during the exclusion period of another clinical study.
- Patient previously randomized in this study.
- Patient being institutionalized because of legal or regulatory order, inmate of psychiatric wards, prison or state institutions, or employee of the study sites or of the sponsor’s company.
- Patient not covered by the government health care scheme of the country in which he/she is living.

- Patient under guardianship/ward of court

Exclusion criteria related to previous and concomitant treatments (medications/non-medicinal therapies/procedures)

- Patient with previous, current prohibited listed treatment (or prohibited modification of treatment regimen).

The prohibited treatments (or prohibited modifications of treatment regimen) and their periods of use prohibition are listed in the following table:

<table>
<tr><td colspan="7">CONCOMITANT MEDICATIONS/NON-MEDICINAL TREATMENTS NOT ALLOWED BEFORE AND DURING THE INVESTIGATION</td></tr>
<tr><td colspan="5">Before the selection visit (Before Day 1-10/Day 1-7)</td><td>Run-in period (From Day 1-10/Day 1-7 to Day 1)</td><td>After randomisation (Day 1 to Day 84)</td></tr>
<tr><td>12 months</td><td>6 months</td><td>3 months</td><td>1 month</td><td>1 week</td><td>Run-in period</td><td>Treatment period</td></tr>
<tr><td colspan="7">Corneal surgery, ...</td></tr>
<tr><td colspan="7">Intraocular injections.....</td></tr>
<tr><td colspan="7">Other ocular surgeries (e.g. cataract, palpebral).....
Isotretinoïde, cyclosporine, tacrolimus, sirolimus, pimecrolimus.....</td></tr>
<tr><td colspan="7">Any change in systemic medication already ongoing before selection visit.....
Permanent punctal plugs.....</td></tr>
<tr><td colspan="7">Semi-permanent or temporary punctal plugs.....</td></tr>
<tr><td colspan="7">Contact lenses.....</td></tr>
<tr><td colspan="5">Any ocular medication other than Hydrabak®</td><td></td></tr>
<tr><td colspan="6"></td><td>Any ocular medication including artificial tears other than authorized medical devices</td></tr>
</table>

2.3 Investigational Medical Devices

T2259

Formulation: Trehalose, 6%; Sodium Hyaluronate, 0.2%

Route of administration: Eye drops

Daily dose regimen: One drop in each eye 2 to 4 times daily

Vismed® Multi

Formulation: Sodium Hyaluronate, 0.18%

Route of administration: Eye drops
Daily dose regimen: One drop in each eye 2 to 4 times daily

2.4 Randomisation

A patient who had given his/her written informed consent and who was included in the study was assigned a specific treatment number.

Random allocation of patients in the T2259 group or Vismed® Multi group assure that all patient's known and unknown characteristics are similar and balanced between groups at the beginning of the study, avoiding the selection bias.

The randomisation code list stratified by site was generated by the CRO in charge of the statistics (AXONAL-BIOSTATEM / independant statistician). Patients were randomised on a 1:1 basis to T2259 or comparator product respectively. The Investigational Medical Device (IMD) was allocated to the patients according to randomisation using an interactive response system (IWRS).

Randomisation occurred at the randomisation visit (Day 1; Visit 2) after all screening procedures had been performed and eligibility for the study confirmed. The patient who met the eligibility criteria was randomly assigned to treatment and associated to a randomisation number.

The treatment number should be recorded in patient's source documents and in the e-CRF.

During the visit 4 (Day 35), this investigator allocated the same treatment number than he did at the randomisation visit.

The treatment number must be recorded in the patient's source document and the e-CRF.

2.5 Study schedule

Table 1: Study Schedule

STUDY PROCEDURE	Visit #1 Selection visit D1-10/D1-7	Run-in period	Visit #2 Randomisation visit D1 (1)		Visit #3 D8 (± 1) Optional visit(6)		Visit #4 D35 (± 3)		Visit #5 Final Visit D84 (± 7) Or Premature withdrawal	
	First ophthalmologist investigator	Preservative free artificial tears Hydrabak®	First ophthalmologist investigator	Second investigator	First ophthalmologist investigator	Second investigator	First ophthalmologist investigator	Second investigator	First ophthalmologist investigator	Second investigator
Informed consent	X									
Demography	X									
Ocular medical and surgical history	X									
Systemic medical and surgical history	X									
Previous and concomitant ocular/non ocular treatments	X		X		X		X		X	
History of Dry Eye	X									
DEQ-5	X						X		X	
OSDI score			X		X		X		X	
Ocular symptoms	X		X		X		X		X	
Ocular symptoms upon instillation(2)						X		X		X
Far best-corrected visual acuity	X						X		X	
Conjunctival hyperaemia (McMonnies photographic scale)	X		X		X		X		X	

Slit lamp examination	X		X		X		X		X	
TBUT	X		X		X		X		X	
Oxford 0-15 grading scheme (corneal staining by fluorescein, temporal and nasal staining by lissamine)	X		X		X		X		X	
Van Bijsterveld score (lissamine green staining)/optional examination [7]	X		X		X		X		X	
Schirmer test (without anaesthesia)			X		X		X		X	
Verification of inclusion/exclusion criteria	X		X							
Tolerance assessment by the investigator							X		X	
Tolerance assessment by the patient							X		X	
Performance assessment by the investigator							X		X	
Urinary pregnancy test [2]	X						X		X	
Adverse events			X		X	X	X	X	X	X
Dispensation of the run-in treatment	X									
Run-in treatment compliance			X							
Dispensation of the IMD [3]				X				X		
IMD compliance [3]								X		X
Evaluation of Optical Scattering Index (OSI) using double pass aberrometry[4]			X				X		X	

Impression cytology (HLA-DR) Only for patients with severe Dry Eye [5]			X						X	

(1) No instillation of preservative free artificial tears (Hydrabak®) at least 6 hours before the randomisation visit.
(2) Urinary pregnancy test to be done for childbearing potential women.
(3) By the second investigator (or the designated site team member) responsible for dispensing, explications of dosing regimen,
(4) The parameters will be measured only in investigator sites equipped with Optical Quality Analysing System (OQAS)
(5) Severe Dry Eye will be defined based on the following criteria: OSDI≥33 and/or Corneal Fluorescein Staining ≥ 3 at the baseline visit (Day 1).
(6) This visit can be performed if the investigator and/or the patient thinks it is necessary.
(7) This examination is not mandatory.

3 STUDY OUTCOME VARIABLES

3.1 Performance criteria

3.1.1 Primary performance endpoint

The primary performance endpoint is change from baseline in total staining grade according to the Oxford 0-15 grading scheme (corneal staining by fluorescein, nasal and temporal conjunctival staining by lissamine green) at Day 35 in the worst eye.

3.1.2 Secondary performance endpoints

Secondary performance endpoints are:

- Change from baseline in total ocular staining grade according to Oxford grading scheme at Day 8 and Day 84 in the worst eye and at Day 8, Day 35 and Day 84 in the contralateral eye;
- Change from baseline in Van Bijsterveld score* (lissamine green staining) at Day 8, Day 35 and Day 84;
- Change from baseline in DEQ-5 at Day 35 and Day 84;
- Change from baseline in OSDI (Ocular Surface Disease Index) score at Day 8, Day 35 and Day 84;
- Change from baseline in Schirmer test result* (without anaesthesia) at Day 8, Day 35 and Day 84;
- Change from baseline in TBUT* (Tear Break-Up Time) at Day 8, Day 35 and Day 84;
- Conjunctival hyperaemia* using McMonnies photographic scale at Day 8, Day 35 and Day 84;
- HLA-DR (AUF) at Day 84 in Right Eye if eligible eye;
- Objective Scatter Index (OSI) at Day 35 and Day 84;
- Dry Eye symptoms: burning/irritation, stinging/eye pain, itching, eye dryness feeling, foreign body sensation, light sensitivity and fluctuating blurred vision evaluated with a 4-level verbal scale (0 = Absent; 1 = Mild, Present but not disturbing; 2 = Moderate, Disturbing, but not limiting daily activities; 3 = Severe, Very distressing and interfering with daily activities) and change from baseline in total score of Dry Eye symptoms at Day 8, Day 35 and Day84;
- Performance assessment by the investigator (Unsatisfactory, Not very satisfactory, Satisfactory, Very satisfactory) at Day 35 and Day 84.

*Assessment recorded for each eye will be analysed for the worst eye and the contralateral eye.

3.2 Safety assessments

Other evaluation parameters are:

- Ocular unusual sensation upon instillation at Day 8, Day 35 and Day 84:

Burning/irritation, stinging/eye pain, itching, eye dryness feeling, foreign body sensation, light sensitivity and other symptoms will be graded by the subject according to the following severity scale and with their duration: (0 = Absent; 1 = Mild, Present but not disturbing; 2 = Moderate, Disturbing, but not limiting daily activities; 3 = Severe, Very distressing and interfering with daily activities);

- Far best-corrected visual acuity (in logMAR) at Day 84;
- Tolerance assessment by the patient and the investigator (Unsatisfactory, Not very satisfactory, Satisfactory, Very satisfactory) at Day 35 and Day 84 ;
- Ocular and systemic adverse events (AE/SAE).

3.3 Derived variables

Source data	Derivation rule	Label	Format
Possible impact of COVID-19 pandemic	If screening visit date (SVSTDT for VISITNUM=1 in SV table) <= 18MAR2020 Then IMPCOVID=0 If screening visit date > 18MAR2020 Then IMPCOVID=1	Possible impact of COVID-19 pandemic	1=”Yes” 0=”No”
Treated eye(s) at D35 and D84	If ECLOCLAT = Right eye, Left eye or Both eyes at least for one visit among Visit D35 and Visit D84, then SS=1 Else SS=0	Safety Set	1=”Yes” 0=”No”
Safety population, randomized status and post baseline performance evaluations	If SS=1 and DSRANDYN=”Y” and at least one post basal value then FAS=1 Else FAS=0 Post basal value include: Oxford scores, Van Bijsterveld scores, DEQ-5 questionnaire, OSDI questionnaire, Schirmer test results, TBUT scores, BCVA, OSI and conjunctival hyperaemia at visit D8, D35 and D84	FAS population	1=”Yes” 0=”No”
FAS population and major deviation	If FAS=1 and MAJDEV=0 Then PP=1 Else PP=0 *MAJDEV refer to major deviation. All major deviations will be determined during the BR meeting*	PP Population	1=”Yes” 0=”No”
Informed consent signed and screen visit performed	If ICYN = "Y" And SVSTDT Ne “” (Where Visitnum=1) Then ENROLLED=1 If ICYN Ne “” Or S VSTDT = “” (Where Visitnum=1) Then ENROLLED=0	Enrolled Population	1=”Yes” 0=”No”
Oxford 0-15 score, Schirmer	To do for both eyes: If 4≤OXFGRTOT≤9 And (3≤ SCHIRM≤9 Or .< TBUTSUM≤30) Then ELIGEYE=1	Eligible eye	1=”Yes” 0=”No”

test and TBUT total score at D1	Else ELIGEYE=0		
Eligible eyes, Oxford scores, Schirmer scores, TBUT total scores at D1	If only one eye is eligible, the eligible eye will be worst eye If both eyes are eligible, then: - Eligible eye will be the eye with the worst Oxford score (maximum score of the eyes) - Else If same Oxford score in both eyes, eligible eye will be the eye with the worst Schirmer score (minimum score of the eyes) - Else If same Schirmer score in both eyes, eligible eye will be the eye with the worst TBUT score (minimum score of the eyes) - Else If same TBUT score in both eyes, eligible eye will be right eye. Else If same schirmer score in both eye, eligible eye will be the Right eye	Worst eye	1=”Right” 2=”Left”
Worst eye	If WORST=1 Then CONTR=2 If WORST=2 Then CONTR=1	Contralateral eye	1=”Right” 2=”Left”
Visit dates at Day 84 and dates of withdrawal	If DSSTAT=”Completed” at the end of the study (visitnum=77, in DS table) Then ENDDT=SVSTDT where visitnum=5 If DSSTAT=”Withdrawal” at the end of the study (visitnum=77, in DS table) Then ENDDT=DSENDDT	End of study date	DDMMMYYYY
Visit dates	FPFV=Min (SVSTDT) where Visitnum=1 FPLV= MIN (ENDDT) LPFV=Max (SVSTDT) where Visitnum=1 LPLV=Max (ENDDT) FPR=Min (SVSTDT) where Visitnum=2 FPR=Max (SVSTDT) where Visitnum=2	FPFV (First Patient First Visit) FPLV (First Patient Last Visit) LPFV (Last Patient First Visit) LPLV (Last Patient Last Visit) FPR (First Patient Randomised)	DDMMMYYYY

		LPR (Last Patient Randomised)	
Visit dates	DURINC=(LPFV-FPFV+1)	Recruitment duration (in days)	Numeric (8.1)
LPLV / FPFV	DURSTYM=(LPLV-FPFV +1) /30.44	Study duration (in months)	Numeric (8.1)
Day 1 and Day 8, 35 and 84 visit dates	BS=Date of D1 SVDELi=(SVSTDATi – BS) i=Days 8, 35 and 84 (data are in line in the table)	Time between D1 and Di (in days)	Numeric (8.1)
Day 1 visit date and onset date of dry eye	DTDRYEYE=INPUT(SUBSTR(MHSTDAT, 1, 4), 8.) DEL_DRYEYE=YEAR(BS) – DTDRYEYE	Time to Dry Eye diagnosis (in years)	Numeric (8.1)
Date of randomisation visit, date and hour of last instillation of Hydrabak	SVSTDT2=dhms(SVSTDT, 0, 0, SVSTTIM) SVSTDAT (when visitnum=2) When ECCAT=”Run-in treatment compliance”: ECENDT2=dhms(ECENDT, 0, 0, ECENTIM)	Date of Day 1 Date and time of last instillation if Hydrabak	DDMMMYYYY DDMMMYYYY HH:MM
Date and time of randomisation and Date and time of last instillation if Hydrabak	TIME_HYD_RD= Intck("Hour", ECENDT2, SVSTDT2)	Time between last instillation of Hydrabak and randomisation visit (hours)	Numeric (8.1)
Start date of Run-In period and End date of Run-In period	When ECCAT=”Run-in treatment compliance” & ECCSPID in (‘1’ ‘’): RUNIN_DUR= (ECENDT – ECSTDT)+1	Treatment duration in run-in period (Hydrabak) (days)	Numeric (8.1)
Treatment dosage respected during the run-in period	When ECCAT=”Run-in treatment compliance” & ECCSPID in (‘1’ ‘’): If ECCOMPYN=”N” Then RICOMPL=0 If ECCOMPYN=”Y” Then RICOMPL=1	Compliance for run-in treatment	0=”No” 1=”Yes”
Start Date of Treatment, End Date of Treatment	DURTT=(ECENDT-ECSTDT)+1 *This derivation rule is valid for D1-D35 and D35-D84 periods*	Treatment period (in days)	Numeric (8.1)
Treatment period (in days) for D1-D35 and D35-D84	DURTT_TOT=SUM(DURTTi) i=D1-D35 and D35-D84 periods *There is one line for D1-D35 period and one line for D35-D84 period. Two lines will be*	Total treatment duration (in days)	Numeric (8.1)

	summed with SQL procedure in order to obtain total treatment period (in days)		
Age at Day 1	If .<AGE<65 Then AGEC=1 If 65≤AGE<85 Then AGEC=2 If AGE≥85 Then AGEC=3	Age (in classes)	1="< 65 years" 2="[65; 85 years[" 3="≥ 85 years"
Date of Selection visit, Date of withdrawal,	STUDY_DUR_D= ENDDT – SVSTDAT (when visitnum=1)+1	Study duration (in days)	Numeric (8.1)
Mean Daily Dose Regimen at D1-D35 and D35-D84 periods	If ECREGIM="2" INSTILLATIONS/DAY" Then ECREGIMn=2 If ECREGIM="3"INSTILLATIONS/DAY" Then ECREGIMn=3 If ECREGIM="4"INSTILLATIONS/DAY" Then ECREGIMn=4 If ECREGIM ="5" INSTILLATIONS/DAY" Then ECREGIMn=5 If ECREGIM="MORE THAN 5" Then Do If exact number of dose are specified in ECREGIMS Then ECREGIMn=Input(ECREGIMS, 8.) If range of number of dose are specified, Then ECREGIMn=Round(mean of the range, 1) As ECREGIMS is a characters variable, mean will be calculated individually *This derivation rule is valid for D1-D35 and D35-D84 periods*	Mean Daily Dose Regimen (n)	Numeric (8.1)
Oxford total score at Day 1, Oxford Total score of the corresponding eye at Days 8, 35 and 84	BSOXFGRTOT=Oxford total score at D1 (OXFGRTOT) EVOL_OXFGRTOTi=(OXFGRTOTi – BSOXFGRTOT) i=Days 8, 35 and 84 (data are in line in the table)	Change from baseline in Oxford Grading Total score on Day i	Numeric (8.1)
Same derivation rule as above for change from baseline in Van Bijsterveld total score (VBGLOBSC and EVOL_ VBGLOBSC)			
Items of DEQ-5 questionnaire at Selection visit, Day 35 and Day 84	If MULTQ51A="" Then DEQ501An=Input(DEQ501A, 8.) If DEQ501A="MISSING%" Or MULTQ51A Ne "" Then DEQ501An=. If MULTQ51B="" Then DEQ501Bn=Input(DEQ501B, 8.)	DEQ-5-Eye discomfort: How often? (n) DEQ-5-Eye discomfort:	Numeric (8.1)

	If DEQ501B="MISSING%" Or MULTQ51B Ne "" Then DEQ501Bn=. If MULTQ52A="" Then DEQ502An=Input(DEQ502A, 8.) If DEQ502A="MISSING%" Or MULTQ52A Ne "" Then DEQ502An=. If MULTQ52B="" Then DEQ502Bn=Input(DEQ502B, 8.) If DEQ502B"MISSING%" Or MULTQ52B Ne "" Then DEQ502Bn=. If MULTQ53="" Then DEQ503n=Input(DEQ503, 8.) If DEQ503="MISSING%" Or MULTQ53 Ne "" Then DEQ503n=. *This derivation rule is valid for Selection visit, Days 35 and 84* *Cases of multi-tick will be discussed during the BR Meeting*	How intense? (n) DEQ-5-Eye dryness: How often? (n) DEQ-5-Eye dryness: How intense? (n) DEQ-5-Watery eyes: How often? (n)	
Items of DEQ-5 questionnaire in numeric format at Selection visit, Day 35 and Day 84	If DEQ501An Ne . And DEQ501Bn Ne . And DEQ502An Ne . And DEQ502Bn Ne . And DEQ503n Ne 1 Then DEQ5TOT=DEQ501An+DEQ501Bn+DEQ502An+ DEQ502Bn+DEQ503n *This derivation rule is valid for Selection visit, Days 35 and 84* *In case of multi-ticked, worst response will be take into account*	DEQ-5-Score (n)	Numeric (8.1)
DEQ-5 total score at Selection visit, DEQ-5 total score at Day 35 and Day 84	BSDEQ5TOT= DEQ5TOT at Selection visit EVOL_DEQ5TOTi = DEQ5TOTi- BSDEQ5TOT i=Days 35 and 84 (data are in line in the table)	Change from baseline in DEQ-5 total score on Day i	Numeric (8.1)
Items of OSDI questionnaire at Days 1, 8, 35 and 84	If MULTOS1= "" Then OSDI0101n=Input(OSDI0101, 8.) If OSDI0101="MISSING%" Or MULTOS1 Ne "" Or OSDI0101="NA" Then OSDI0101n=. If MULTOS2="" Then OSDI0102n=Input(OSDI0102, 8.) If OSDI0102="MISSING%" Or MULTOS2 Ne ""Or OSDI0102="NA" Then OSDI0102n=. …	OSDI-Eyes Sensitive to Light OSDI-Eyes Gritty …	Numeric (8.1)

	If MULTOS12="" OSDI0112n=Input(OSDI0112, 8.) If OSDI0112="MISSING%" Or MULTOS12 Ne "" Or OSDI0112="NA" Then OSDI0112n=. *This derivation rule is valid for Days 1, 8, 35 and 84* *Cases of multi-tick will be discussed during the BR Meeting* *In case of multi-ticked, worst response will be take into account*	OSDI-Air Conditioned Areas	
Items of OSDI questionnaire in numeric format at Days 1, 8, 35 and 84	OSDI0113b=SUM(OSDI0101n, n, OSDI0103n, OSDI0104n, OSDI0105n) OSDI0114b=SUM(OSDI0106n, OSDI0107n, OSDI0108n, OSDI0109n) OSDI0115b=SUM(OSDI0110n, OSDI0111n, OSDI0112n) *This derivation rule is valid for Days1, 8, 35 and 84*	OSDI-Subtotal Score Answers 1 to 5 OSDI-Subtotal Score Answers 6 to 9 OSDI-Subtotal Score Answers 10 to 12	Numeric (8.1)
Subtotal Score Answers 1 to 5, OSDI-Subtotal Score Answers 6 to 9, OSDI-Subtotal Score Answers 10 to 12 at Days 1, 8, 35 and 84	NBOSDI=Total number of questions answered (without NA answered) OSDITOT=SUM(OSDI0113b,OSDI0114b, OSDI0115b) OSDI0118b=(OSDITOT*25)/NBOSDI *This derivation rule is valid for Days 1, 8, 35 and 84*	Number of questions answered OSDI-Total Sum OSDI-Total Score Re-Calculated	Numeric (8.1)
OSDI total score at Day 1, OSDI total score at D	BSOSDI0118b = OSDI0118b at D1 EVOL_OSDI0118bi = OSDI0118bi-BSOSDI0118b i=Days 8, 35 and 84 (data are in line in the table)	Change from baseline in OSDI total score on Day i	Numeric (8.1)
OSDI total score at Days 1, 8, 35 and 84	If 0≤ OSDI0118b <13 then OSDI0118c=1 If 13≤ OSDI0118b <23 then OSDI0118c=2	OSDI total score (classes)	1="Normal" 2="Mild" 3="Moderate" 4="Severe"

	If 23≤ OSDI0118b <33 then OSDI0118c=3 If 33≤ OSDI0118b ≤100 then OSDI0118c=4 *This derivation rule is valid for Days 1, 8, 35 and 84* *In statistical results, range of each modality will be specified with footnote*		
Schirmer test result at Day 1, Schirmer test result of the corresponding eye at Days 8, 35 and 84	BSSCHIRM= Schirmer test result at D1 (SCHIRM) EVOL_SCHIRMi=(SCHIRMi – BS SCHIRM) i=Days 8, 35 and 84 (data are in line in the table)	Change from baseline in Schirmer test result on Day i	Numeric (8.1)
TBUT measurements 1, 2 and 3 at Days 1, 8, 35 and 84	MEANTBUT=(TBUT1+TBUT2+TBUT3)/3 *This derivation rule is valid for Days 1, 8, 35 and 84*	Mean TBUT	Numeric (8.1)
Mean TBUT at Day 1, Mean TBUT of the corresponding eye at Days 8, 35 and 84	BSMEANTBUT= Mean TBUT at D1 (MEANTBUT) EVOL_MEANTBUTi=(MEANTBUTi – BS MEANTBUT) i=Days 8, 35 and 84 (data are in line in the table)	Change from baseline in Mean TBUT on Day i	Numeric (8.1)
Severity/Intensity of Dry Eye Symptoms at each visit	If CESEV="ABSENT" Then CESEVn=0 If CESEV="MILD, PRESENT BUT NOT DISTURBING" Then CESEVn=1 If CESEV="MODERATE, DISTURBING, BUT NOT LIMITING DAILY ACTIVITIES" Then CESEVn=2 If CESEV="SEVERE, VERY DISTRESSING AND INTERFERING WITH DAILY ACTIVITIES" Then CESEVn=3	Severity / Intensity (n)	0=”Absent” 1=”Mild” 2=”Moderate” 3=”Severe”
Dry Eye Symptoms	If, for the visit i patient does not have all symptoms, missing symptoms will be created with CESEVn=0 Only for CECAT=”Ocular Symptoms”	Severity / Intensity (n)	0=”Absent” 1=”Mild” 2=”Moderate” 3=”Severe”
Dry eye symptoms at each visit	SCORE_DES=Sum(CESEVn) Where CECAT=Ocular Symptoms *Only for the 7 predefined dry eye symptoms and if the 7 predefined dry eye symptoms are not missing*	Total score of Dry Eye symptoms	Numeric (8.1)

The 7 predefined dry eye symptoms are: Burning/Irritation, Stinging/Eye pain, Itching, Eye dryness feeling, Foreign body sensation, Light sensitivity and Fluctuating blurred vision			
Total score of Dry Eye symptoms at Days 1, 8, 35 and 84	BS SCORE_DES= Total score of Dry Eye Symptoms at D1 (SCORE_DES) EVOL_SCORE_DESi=(SCORE_DESi– BSSCORE_DES) i=Days 8, 35 and 84 (data are in line in the table)	Change from baseline in total score of dry eye symptoms on Day i	Numeric (8.1)
Change from baseline in total score of dry eye symptoms on Day 8 (i.e. Days 35 and 84)	If .Z<EVOL_SCORE_DESi<0 Then EVOL_SCORE_DESCi=1 If EVOL_SCORE_DESi=0 Then EVOL_SCORE_DESCi=2 EVOL_SCORE_DESi>0 Then EVOL_SCORE_DESCi=3 i=Days 8, 35 and 84 (data are in line in the table)	Evolution Dry Eye symptom on Day i	1=”Improvement” 2=”Stable” 3=”Worsening”
Symptoms upon instillation	If, for the visit i patient does not have symptoms upon instillation, 6 lines will be created for the 6 predefined symptoms, with CESEVn=0 Only for CECAT=”Ocular Symptoms Upon Instillation”	Severity / Intensity (n)	0=”Absent” 1=”Mild” 2=”Moderate” 3=”Severe”
Symptoms upon instillation	SCORE_UPON= Sum(CESEVn) Where CECAT= Ocular Symptoms Upon Instillation *Only for the 6 predefined dry eye symptoms and if the 6 predefined dry eye symptoms are not missing*	Total score of unusual sensation UPON INSTILLATION	Numeric (8.1)
The 6 predefined dry eye symptoms are: Burning/Irritation, Stinging/Eye pain, Itching, Eye dryness feeling, Foreign body sensation and Fluctuating blurred vision			
Start of previous and concomitant treatments	If substr(CMSTDAT, 9, 2)=”ND” then the day will be replaced by 01 (first day of the month) If substr(CMSTDAT, 6, 5)=”ND/ND” then the month and the day will be replaced by 01/01 (first day of the year Name of the created variable: CMSTDATimp	Start date of medications (imputed, n) *Will be used only to determined type of treatment (previous, concomitant or post-study)*	DDMMMYYY
End date of previous and	If substr(CMENDAT, 9, 2)=”ND” then the day will be replaced by 28, 30 or 31, depending of the month (last day of the	End date of medication (imputed, n)	

concomitant treatments	month) If substr(CMENDAT, 6, 5)=”ND/ND” then the month and the day will be replaced by “12/31” (last day of the year) Name of the created variable: CMENDATimp	*Will be used only to determined type of treatment (previous, concomitant or post-study)*	
Start date and End date of previous and concomitant treatments	If CMSTDT Ne . And CMENDT Ne . Then PCM_DUR=((CMENDT-CMSTDT)+1)/30.44 If CMONGO=”Y” Then PCM_DUR=.	Duration of treatment (in months)	Numeric (8.1)
Start date and end date of previous and concomitant treatments	If CMSTDATimp Ne . And CMENDATimp Ne . Then PCM_DUR=((CMENDATimp - CMSTDATimp)+1)/30.44 If CMONGO=”Y” Then PCM_DUR=.	Duration of treatment (in months, with imputed dates)	Numeric (8.1)
Date of Instillation at Day 1	DAKDATD1=Date of instillation at D1 (VISITNUM=2)	Date of treatment initiation	DDMMMYYYY
Date of last instillation	DAKDATLAST=Max(DAKDT)	Date of last treatment dispensation	DDMMMYYYY
Imputed start date and end date of previous and concomitant treatment and date of selection visit	If CMENDAT_dat Ne . And DAKDATD1 Ne . And CMENDAT_dat<DAKDATD1 Then CMTYP=1 If CMSTDAT_dat Ne . And DAKDATLAST Ne . And CMSTDAT_dat>DAKDATLAST Then CMTYP=3 If CMENDAT_dat Ne . And DAKDATD1 Ne . And CMENDAT_dat>=DAKDATD1 Then CMTYP=2 <u>In case of ongoing with start date available:</u> If CMTYP=. And CMONGO="Y" And CMSTDAT_dat Ne . And CMSTDAT_dat<DAKDATLAST Then CMTYP=2 <u>In case of no start date of medication:</u> If CMSTDAT_dat=. And DAKDATD1 Ne . Then CMTYP=2 <u>If no date of treatment initiation:</u> If DAKDATD1=. Then CMTYP=.	Type of medication (previous or concomitant)	1=”Previous” 2=”Concomitant” 3=”Post-study”

	Medications without type will be reviewed during the BR Meeting		
HLA-DR at Day 1 and Day 84	LBHLAREL2=LBHLAREL If LBYN=”Y” And LBVAL="N" Then LBHLAREL2=.	HLA-DR positive cells (%, missing for invalid result)	Numeric (8.1)
Tolerance assessment by the investigator at Day 35 and Day 84	IF TOLERI In (‘SATISFACTORY’ ‘VERY SATISFACTORY’) Then TOLERI2=1 If TOLERI In (‘NOT VERY SATISFACTORY’ ‘UNSATISFACTORY’) Then TOLERI2=2 *This derivation rule is valid for Days 35 and 84*	Tolerance assessment by the investigator	1=”Very satisfactory / Satisfactory” 2=”Not very satisfactory / Unsatisfactory”
AE start date, AE end date	AEDUR=(AEENDT – AESTDT)+1 only if AEOUT=” RECOVERED/RESOLVED”	AE duration (in days)	Numeric (8.1)
AE start date, Start date of treatment	AETIME=(AESTDT – DAKDATD1)	AE onset from First IMD instillation (days)	Numeric (8.1)
Start date of treatment / Time of onset of AE	If AESTDT < DAKDATD1 then TEAE=0 If AESTDT >= DAKDATD1 then TEAE=1 *In case of missing or uncompleted onset date/time, the status will be defined during the Blind Review (BR) meeting according to the information recorded in other fields*	Treatment Emergent Adverse Event (TEAE)	0=”No” 1=”Yes”
AE type and localisation	If TEAE=1 And localisation in ("BOTH EYES" "RIGHT EYE" "LEFT EYE") Then OCTEAE=1 If (TEAE=1 And AELOCLAT="OTHER") Or TEAE=0 Then OCTEAE=0	Ocular TEAE	0=”No” 1=”Yes”
AE type and causality	If TEAE=1 And AEREL=”RELATED” Then ADE=1 If TEAE=0 Or (TEAE=1 And AEREL="NOT RELATED") Then ADE=0	ADE	0=”No” 1=”Yes”
AE type and serious event	If ADE=1 And AESER =”Y” Then SADE=1 If ADE=0 Or (ADE=1 And AESER="N") Then SADE=0	SADE	0=”No” 1=”Yes”
AE type and Action Taken with Study Treatment	If TEAE=1 And AEACN ”drug withdrawn” Then WTEAE=1 Else WTEAE=0	TEAE leading to Medical Device withdrawal	0=”No” 1=”Yes”

4 SEQUENCE OF PLANNED ANALYSES

4.1 Interim analyses

No interim analysis is planned.

4.2 Final analyses and reporting

This SAP described the final statistical analysis.

The analyses will be performed after the database has been cleaned and locked.

A BR meeting will be conducted prior to database lock. Treatment allocations will not be un-blinded and no un-blinded analyses will begin until this SAP has been approved by the sponsor.

Any post-hoc exploratory analyses performed to provide support for planned analyses but not identified in this SAP will be documented and reported in appendices to the CSR and clearly identified as unplanned analyses in the text of the CSR.

4.3 Changes to statistical information in the clinical trial protocol

In the protocol, the final visit form can either be D84 visit or Withdrawal visit. Withdrawal visits specified in the final visit form will be reviewed during the BR meeting and reclassified to the closest missing planed timepoint (D8, D35 or D84).

Information collected during withdrawal visit will be used in the analysis as reclassified visit.

In the protocol, for the primary performance endpoint, the investigator site and the investigation product-by investigator site interaction was expected to be explored as a secondary analysis prior to presenting the final model. As the number of randomised patients by site is low, investigator site will not be tested but replaced by country effect.

For the primary performance endpoint, additional sensitivity analysis will be performed: Mixed Model for Repeated Measures (MMRM) model will be used including: treatment group, baseline value, visit, treatment group by visit interaction and treatment group by baseline value interaction.

To investigate the bias of recruitment before and after the recruitment interruption, patients will be classified without or with possible impact of COVID-19 pandemic based on their screening visit date respectively up to and including 18 MARS, or after the 18-MAR-2020. Descriptive analysis will be performed according to this variable (populations, countries, premature withdrawal, protocol deviations and demographic characteristics (age and sex). Moreover, for the primary endpoint, an exploratory model will be performed using initial model, adjusted on this new variable.

For the analysis of previous and concomitant medications, ATC level 2 and 4 will be used, instead of level 3 and 4 specified in the protocol.

For performance and tolerance assessment, Wilcoxon signed-rank test will be replaced by Cochran-Mantel-Haenszel (CMH) test, and Chi-2 test for Dry Eye Symptoms will be replaced by Cochran-Mantel-Haenszel (CMH) test.

In the safety endpoints, for the comparison between treatment group of the total score of the 6 predefined symptoms (unusual sensation upon instillation), Student T-test will be performed, instead of the use of Analysis of Covariance (ANCOVA) analysis as specify in the protocol. Student T-test will be performed if the normality of the data is verified. If the data have not normal distribution, Mann-Whitney Wilcoxon test will be used.

5 STATISTICAL METHODOLOGY

5.1 Detailed power and sample size

The aim of the study is to demonstrate the non-inferiority of T2259 with regard to Vismed® Multi in terms of performance. The primary performance criterion is the change from baseline of total ocular staining grade in the worst eye on Day 35, evaluated using Oxford 0-15 grading scheme.

As the statistical hypothesis is the non-inferiority of T2259 with regard to Vismed®, the main analysis of the primary criterion will be performed in the Per Protocol population.

A total of 76 patients (i.e. 38 per treatment group) assume at least 90% power to establish the non-inferiority comparison on a one sided two sample t test with α=2.5 % basis (equivalent to a 95% two sided confidence interval), assuming that the standard deviation is 2.5 and no difference between the 2 groups with a non-inferiority limit set at 2 for the change in total ocular staining grade.

Estimation of the standard deviation and determination of the non-inferiority limit are based upon data of previous studies and literature.

Concerning the non-inferiority limit, according to clinicians, a variation of 2 points in the total Oxford grade, which corresponds to a variation of less than 1 grade in the three areas (corneal, temporal and nasal), is considered as not clinically significant.

For taking into account approximately 15% of patients non—evaluable in Per protocol analysis (premature withdrawals without performance evaluation, patients with major protocol deviation), a total of 90 patients should be randomised in the study.

The non-evaluable patient rate was based on the previous studies major deviations and missing data. For this study, missing data are higher than planned (partially due to Covid-19 pandemia) and the number of randomised patients is 101 to maintain approximately the number of 76 patients evaluable in the Per Protocol.

5.2 Generalities for statistical analyses

After the database lock and the randomisation code release, the statistical analysis will be performed by the statistician of Axonal-Biostatem, using SAS® software v9.4 (GUIDE, SAS Institute, North Caroline, USA), according to this SAP.

Disposition and baseline characteristics will be presented overall (globally) and by treatment groups. Performance and safety assessments and exposure/compliance will be presented by treatment groups.

Continuous variables will be summarised using descriptive statistics (number of non-missing data (n), number of missing observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum).

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

To compare treatment groups for ordinal qualitative variables, Cochran-Mantel-Haenszel (CMH) test will be used stratified by baseline values (if mentioned), with modified ridit scores and “row mean score differ” option. To compare treatment group when variable will be quantitative, Student T-test will be used, when data distribution will be assumed as normal (Shapiro-Wilk test for normality). If it is not the case, Mann-Whitney Wilcoxon test will be preferred instead.

Quantitative parameters will be also compared between groups using ANCOVA model. Furthermore, the mean change from baseline in total staining grade in the worst eye at Day 35 will be compared between the two treatments based on the MMRM analysis, which assumes:

- Data are Missing At Random (MAR)
- All the available data provide the information about non-observed data
- The treatment effect assume that the withdrawn patients mimic those who continued

Assumptions underlying the ANCOVA (respectively MMRM for the sensitivity analysis) will be checked:

- A histogram of residuals will be plotted to check the assumption of normality
- The underlying assumptions of normality of residuals will also be checked by using Shapiro-Wilk test
- Normal probability plot and QQ-plot will be performed to check the assumption of normality
- Residuals will be plotted against predicted values to check the assumption of heteroscedasticity
- For ANCOVA models, Levene's test will also be performed to check the homogeneity of variances

For each model (MMRM or ANCOVA) if there is a strong violation of normality assumption, a non-parametric comparison – Wilcoxon Rank Sum Test – will be performed in addition to the initial model.

Frequency distribution (number of non-missing observations (n), count and percentage of each modality,) will be summarized for the categorical variables.

All percentages should be rounded and reported to a single decimal place (xx.x%).

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).

Assessment recorded for both eyes will be presented for the worst eye and for the contralateral eye.

Baseline will be defined as the last value before the first instillation.

Change from baseline is defined as the change from the last assessment before the first instillation of the IMD.

However, if measurements are repeated before and after each instillation, baseline is defined as the assessment before the concerned instillation. In this case, the changes from baseline are defined from values assessed after the IMD intake minus the baseline values (last assessment before concerned IMD).

Time between two dates will be calculated as latest date minus earliest date. Study days prior to first injection date are calculated as (actual date – first injection date), after first injection date as (actual date – first injection date) + 1.

All patient data listings will be edited separately. The subject ID, the concerned eye (Right eye/Left eye), the worst eye (Right eye/Left eye), the treatment group, the visit (if applicable) will be presented as identifier variables. Analysis populations for each patient will appear in all the listings.

All patient data listings described in Section 11.9.2 of Clinical Investigation Report will be edited for all the recorded assessments and derived data by type of parameters: Disposition, Demography, Medical history, Previous and Concomitant treatments, Other baseline characteristics (all assessments recorded only at baseline), Performance assessments and endpoints, Safety examinations – by visit, Adverse event, exposure to treatments (Hydrabak®, T2259, Vismed® Multi), Compliance.

Data listings will be presented sorted by subject ID, eye (if applicable) and timepoint (visit).

All date fields will be presented in a format of ddmmmyyyy (e.g., 01Jan2004) in the listings.

5.3 Multiple Imputations for Handling of Dropouts or Missing data

Treatment Emergent Adverse Events (TEAEs) are AEs that occurred after the first IMD instillation. AEs that occurred the day of the first IMD instillation will be reviewed in detail to identify if AEs appeared before or after the first treatment with IMD (to decide if they have to be considered as TEAEs or not). If no additional information is available, they will be treated as TEAEs.

By default, AEs will be considered as TEAEs if no enough information is available.

For primary analysis performed on FAS, Last Observation Carried Forward (LOCF) method will be applied in case of missing value.

In order to define the type of treatments (previous, concomitant or post-study) and treatment duration, partially start/end dates will be imputed with the following rules for calculations:

<u>For treatment start date:</u>

- If only the day is missing, it will be considered as 1st for calculations
- If only the year is completed, day and month will be considered as January 1st for calculations

For treatment end date:

- If only the day is missing, it will be considered as the last day of the month for calculations
- If only the year is completed, day and month will be considered as December 31st for calculations

If the date is totally missing, it will not be replaced.
Other missing data will not be replaced.

5.4 Adjustments for Covariates

For the primary analysis, ANCOVA model will be constructed including investigation product as factor and Oxford total score at baseline (Day1) as continuous covariate.

Country and the investigation product-by country interaction will be in addition explored as a secondary analysis prior to presenting the final model.

Moreover, for the primary endpoint, in MMRM analysis (sensitivity analysis), investigation product, Oxford total score at baseline (Day1), visit, investigation product by visit interaction and Oxford total score at baseline by visit interaction will be in the model.

As sensitivity analysis, for the primary endpoint, possible impact of COVID-19 and investigation product by possible impact of COVID-19 will be added in the ANCOVA model.

There is a single primary performance endpoint in the study (change from baseline in the ocular staining grade at D35 in the worst eye) and non-inferiority will be concluded if it is achieved. Other performance endpoints are defined to be of secondary importance. Thus comparison will be performed at a two-sided significant level of 5% and no adjustment of the type I error will be made.

5.5 Multicentre

The investigation was carried out in France, in Spain, in Slovakia and in Poland.

6 STATISTICAL ANALYSES

6.1 Study Populations

6.1.1 Protocol Deviations

Protocol deviations will be reviewed during the BR meeting and defined as minor and major deviations. The patients with major deviations will be excluded from the Per protocol population.

The decisions taken by the BR committee will be recorded in the BR meeting minutes.

Furthermore, all minor and major deviations will be recorded in the database: a datafile with all patients and information pertaining to analysis sets and protocol deviations will be created according to BR decisions.

The database will be locked after validation of the BR meeting minutes. A certificate of data lock will be provided, then the blind will be broken, and the analyses will be carried out according to the SAP.

6.1.2 Analysis Populations

Full Analysis Set (FAS) will be composed of all randomised patients (according to ITT principle, i.e. analysed based on the initial treatment assignment), having used at least one dose of investigation medication and for whom at least one post-baseline performance evaluation will be available.

Per protocol set (PP) will be a subset of the FAS without major protocol deviation. The precise reasons for excluding patients from the PP set will be defined and documented before breaking the blind during the BR meeting.

Safety population (SAF) will be composed of all patients exposed to the investigation Medical Device, i.e. having used at least one administration of the investigational Medical Device.

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

The **Eligible Eye** will be defined by following conditions:

- Oxford 0-15 score ≥ 4 and ≤ 9 AND;
- At least one of the following objective signs:
  - Schirmer test ≥ 3 mm/5 min and ≤ 9 mm/5 min, **Or**
  - Sum of 3 TBUT measurements ≤ 30 seconds.
  - **And** without ophthalmological exclusion criterion

For patient with one eligible eye, this eye is considered as the “Worst eye” (study eye for primary analysis).

For patients with both eligible eyes or no eligible eye, the **Worst Eye** will be:

- Eye with the worst Oxford score;
- If same Oxford score in both eyes: eye with the worst Schirmer score;
- If same Oxford and Schirmer scores in both eyes: eye with the worst TBUT score;
- If same Oxford, Schirmer and TBUT scores in both eyes: right eye.

Note: worse Oxford score means highest value, whereas worse Schirmer score or worse TBUT score means lowest value.

The opposite to the worst eye is the **Contralateral Eye**.

Eligible eyes and Worst eye will be validated during the BR.

6.2 Disposition of Patients

Descriptive statistics will be provided. No statistical test will be performed.

- Study dates: first date and last date will be provided for selection visit, inclusion visit and last visit (visit 5 or early withdrawal).
- Number and percentage of patients in each country and each site will be provided in FAS and Safety set.
- Status of patients:
  - Among all patients: number and percentage of patients selected and not selected, reason if not selected (as reported by the investigator at the selection visit)
  - Among selected patients: number and percentage of patients who attended inclusion visit, number and percentage of patients included and not included, reason if not included (as reported by the investigator on end-of-study page: Adverse event, lack of performance, withdrawal by subject, lost to follow-up, screen failure, other)
  - Among included patients: randomised (Yes, No)
  - Among randomised patients: number and percentage of patients with visits done (for each visit: Yes, No), visit type if Visit 5 done (Day 84 +/-7 days, Premature discontinuation visit), has the patient completed the study (Yes, No), reason if study not completed (Adverse event, lack of performance, withdrawal by subject, lost to follow-up, screen failure, other)

  Non-selected patients, non-included patients and early withdrawals will be individually listed.

  Note: In case of withdrawal, withdrawal visit will be re-assigned depending to the date of withdrawal. The withdrawal visit will be re-assigned to the closest planned missing visit (D8, D35 or D84). All re-assigned withdrawal visits will be discussed during BR and recorded in the BR meeting minutes.

- Analysis sets:
  - From randomised patients: Number and percentage in safety population, number and percentage of patients excluded from safety population and reason(s) for exclusion
  - From safety population: Number and percentage in FAS, number and percentage of patients excluded from FAS and reason(s) for exclusion
  - From FAS: Number and percentage in PP, number and percentage of patients excluded from PP and reason(s) for exclusion
  - Number and percentage of patients with major and minor protocol deviations, globally and for each section of deviation (inclusion criteria deviation, exclusion criteria deviation, randomisation, visit windows and chronology, run-in treatment compliance, IMD compliance, primary performance endpoint and secondary efficacy endpoints, other), in FAS.

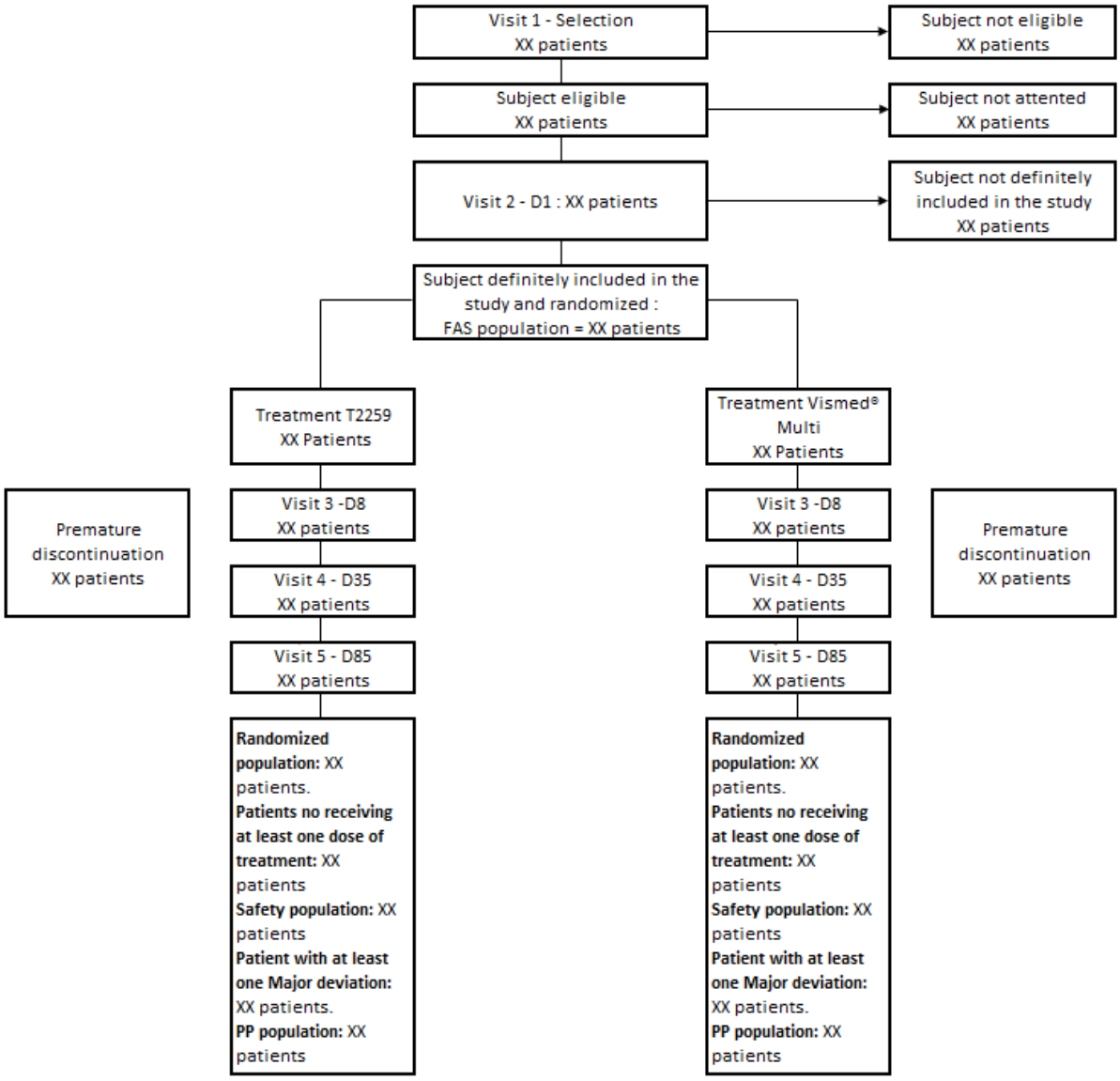
Minor and major deviations will be individually listed, an exhaustive data listing of all patients and information pertaining to analysis sets will also be provided.

- Time between visits: time from inclusion visit will be described at selection visit and post-inclusion visits in FAS. For time between randomisation (inclusion) visit date and selection visit date: Randomisation visit date (Day 1) – Selection visit date. For Day 8, Day 35 and D84 it will be calculated as follow: D8 / D35 / D84 visit date – Randomisation visit Date (Day 1).

  Time from inclusion visit to Visit 5 will be provided separately for patients for whom visit 5 = Day 84 +/7 days and for patients for whom Visit 5 is a premature discontinuation visit.

- Study duration will be described in FAS.

Patients accountability will be described thanks to the flowchart below:



6.3 Demographic and Baseline Characteristics

Parameters below will be described globally and by treatment group on PP population and FAS, and Safety population if it differs from FAS.

- Demographic data
  - Sex
  - Age
  - Age in classes (<65 years old, >=65 and < 85 years old, >= 85 years old)

- Baseline characteristics (at selection and randomization visits) will be displayed in the performance tables, as described in the Section 6.7.

- History of dry eye
  - Time from the Dry eye diagnosis (calculated at selection visit)
  - Aetiology of the dry eye (primary/secondary Sjögren syndrome/Meibomian gland deficiency/Non-Sjögren aqueous deficiency/other)
    A listing of other aetiology will be produced.
  - Eligible eye (none/right eye/left eye/both eyes)
  - Worse eye (right eye/left eye)

- Medical and surgical history

Medical and surgical history has been coded with MedDRA dictionary (version 22.0).

The number and percentage of patients experiencing at least one medical or surgical history will be provided, overall and by MedDRA primary SOC and PT, separately for ocular medical history other than the studied disease, ocular surgery history other than the studied disease, systemic medical history other than the studied disease and systemic surgery history other than the studied disease.

Note: Results will be provided by descending frequency (for SOCs and for PTs within SOC, for the whole population analysed)

6.4 Subgroup analysis

Patients will be classified without or with possible impact of COVID-19 pandemic based on their Selection visit date respectively up to and including 18-MARS-2020, or after the 18-MAR-2020. The following summaries will be performed:

- Number (%) of patients in each analysis set and reasons for exclusion by possible impact of COVID19
- Number (%) of patients in each country by possible impact of COVID-19
- Number (%) of premature withdrawal by possible impact of COVID-19
- Protocol deviations by possible impact of COVID-19
- Demographic characteristics by possible impact of COVID-19

Analysis sets will be presented on all randomised subjects, protocol deviation on FAS population, whereas countries, premature withdrawal and demographic characteristics will be presented on FAS and SAF populations.

6.5 Previous, Concomitant and Post-Study Medications

Previous and concomitant medication will be described overall and by treatment group in the FAS and the PP, separately for ocular and non-ocular treatments.

Treatments have been coded using the WHO Drug Dictionary Enhanced (WHODrug: B3 Global 2018Q3)

Number and percentage of patients with at least one previous or concomitant treatment will be presented overall and by ATC classification level 2 and ATC classification level 4, according to the 3 observation periods:

- Previous treatments: Treatments ended before the first instillation of the IMD or the same day
- Post-study treatment: Treatments started after the last instillation of IMD or the same day
- Concomitant treatments: Treatments started between the first and last instillation of the IMD (or the same day) or treatments started before the first instillation of the IMD and ended after the first instillation of the IMD.

Note: Results will be provided by descending frequency (for ATC classification level 2 and ATC classification level 4 with level 2, for the whole population analysed)

The Individual data listing will present all CRF items and calculated variables as treatment duration and periods (previous, post-study or concomitant treatment).

6.6 Treatment exposure and compliance

The following variables will be described by treatment group, in the Safety population, the FAS and the PP, without performing any statistical test:

- Treatment duration in run-in period (Hydrabak) (days): quantitatively
  - = Date of the last instillation of Hydrabak – Date of the first instillation of Hydrabak + 1
- Time between last instillation of Hydrabak and inclusion visit date (hours): quantitatively
- Run-in treatment compliance: dosage for Hydrabak respected? (Yes, No)
- Study treatment duration (days): quantitatively, for the whole study and separately for D1-D35 and D35-D84 periods
- Mean daily dose regimen: quantitatively and in classes (0, 1, 2, 3, 4, 5, >5) during all the study and separately for D1-D35 and D35-D84 periods

  When dose regimens are equal to “more than 5 instillation/days”, it will be reviewed and converted into numeric values. In case of range, mean range value rounded to the integer will be used. Patients without any treated eye will have 0 for the mean daily dose regimen.

Patients for whom mean daily dose regimen was different from 2 to 4 instillations/day will be individually listed (treatment dates at each visit, mean daily regimen, comments).

6.7 Performance analyses

6.7.1 Primary Performance Endpoint

Primary performance endpoint will be analysed only in the worst eye.

Descriptive tables will be produced presenting selection, baseline (D1), Day 8, Day 35 and Day 84 Oxford Total score and change from baseline for Oxford Total score at Day 8, Day 35 and Day 84.

Oxford grade at each visit and change from baseline at Day 8, Day 35 and Day 84 will be also described for each panel: temporal bulbar conjunctiva, corneal area and nasal bulbar conjunctiva.

The hypothesis of non-inferiority of T2259 compared to Vismed® Multi will be tested by calculating the bilateral 95% CI of the difference between groups (T2259 – Vismed® Multi) of the change from baseline of Oxford Total Score on Day 35. A two-way analysis of covariance (ANCOVA) model will be constructed using main effects of investigation product and baseline score as covariate. Adjusted means by investigation product will be presented as well as an estimate of the difference between adjusted means.

A 95% two-sided confidence interval, based on the ANCOVA model (2), will be computed for the difference of T2259 minus Vismed® Multi. If the upper bound is no higher than 2 points for the PP population, it will be concluded that the null hypothesis can be rejected and that T2259 is non-inferior to Vismed® Multi.

The result will be presented as follow:

Population	T2259 (N=XX)	Vismed® Multi (N=XX)	Difference T2259 – Vismed Multi	SE of Difference T2259 – Vismed Multi	95% CI
Day 1 (baseline) mean (SD)	X1	Y1			
Day 35 mean (SD)	X2	Y2			
Adjusted mean change (SE) between Day 1 and Day 35	[X2-X1]*(SE)	[Y2-Y1]*(SE)	[X2-X1] -[Y2-Y1]	SE	[Min - **Max**]

* These values were expected as negative, meaning an improvement of the Oxford score.
** The upper bound indicates the maximal difference of change in disfavour of T2259.

This analysis will be performed firstly on the Per Protocol population on the observed data.

Same analysis will be performed on FAS population with imputation of values in case of missing data with LOCF technique (Day 8 or value in case of withdrawal) and without imputation (observed cases) for confirmation.

The country and the investigation product-by-country interaction will be explored as a secondary analysis prior to presenting the final model (1).

Same analysis as principal analysis (ANCOVA model) will be performed adjusted on possible impact of COVID-19 pandemic (3).

Another sensitivity analysis will be performed using MMRM model (4). This model will be constructed using main effects of investigation product and visit as factors and total Oxford baseline score as continuous covariate. Interactions between treatment and visit, treatment and baseline total Oxford score will also be included. REML method will be used and the covariance structure will be defined as unstructured: unstructured approach makes no assumption about the correlations among visits. If the analysis fails to converge, then spatial covariance, compound symmetry, or first order autoregressive model (A1) structure will be used. The best model fit will be determined by the AIC.

For the ANCOVA and MMRM analyses, the following MIXED procedure (SAS®) will be used.

Model	Method	SAS code

(1)	ANCOVA	`PROC MIXED DATA=XX ORDER=DATA;`
		`WHERE PP = 1; /* OR FAS=1 */`
		`CLASS TT COUNTRY;`
		`MODEL EVOL = TT BASELINE COUNTRY TT*COUNTRY /`
		`SOLUTION ALPHA=0.05; /* OTHER CHARACTERISTICS CAN BE ADDED HERE */`
		`LSMEANS TT / DIFF=CONTROL CL OM;`
		`RUN;`

(2)	ANCOVA	Final model:
		`PROC MIXED DATA=XX ORDER=DATA;`
		`WHERE PP = 1; /* OR FAS=1 */`
		`CLASS TT;`
		`MODEL EVOL = TT BASELINE / SOLUTION ALPHA=0.05;`
		`/* OTHER CHARACTERISTICS CAN BE ADDED HERE */`
		`LSMEANS TT / DIFF=CONTROL CL OM;`
		`RUN;`

(3)	ANCOVA	`PROC MIXED DATA=XX ORDER=DATA;`
		`WHERE PP = 1; /* OR FAS=1 */`
		`CLASS TT COVID;`
		`MODEL EVOL = TT BASELINE COVID TT*COVID/ SOLUTION ALPHA=0.05; /* OTHER CHARACTERISTICS CAN BE ADDED HERE */`
		`LSMEANS TT / DIFF=CONTROL CL OM;`
		`RUN;`

(4)	MMRM	`PROC MIXED DATA=XX METHOD=REML;`
		`WHERE PP=1; /* OR FAS=1 */`
		`CLASS TT SUBJID VIS;`
		`MODEL EVOL = TT VIS BASELINE TT*VIS BASELINE*VIS / DDFM=SATTERTH SOLUTION ALPHA=0.05;`
		`REPEATED VISIT / TYPE=UN SUBJECT=SUBJID;`
		`LSMEANS TT*VIS / PDIFF CL;`

```
        ESTIMATE "D35 (VISIT 4) - DIFF T2259 - VISMED"
        TREATMENT 1 -1
        VISIT*TT 0 1 0   0 -1 0 / CL;
        ODS OUTPUT LSMEANS=MEANS DIFFS=DIF;
RUN;
```

6.7.2 Secondary Performance Endpoints

Secondary performance endpoints analysis will be provided in the PP population and the FAS population and for both worse eye and contralateral eye.

- Oxford total score

Descriptive summaries for the Oxford Total score, change from baseline and summaries by panel will be repeated for the contralateral eye in the same manner as for the Primary Endpoint analysis.

Change from baseline in Oxford total score at D8 and D84 on worst eye and at D8, D35 and D84 in contralateral eye will be analysed using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

- Van Bijsterveld score* (lissamine green staining)

All items used to calculate the total score will be tabulated, by treatment group, with frequency and percentage at each time point (Selection visit, D1, D8, D35 and D84). Total score and change from baseline will be tabulated, by treatment group, with all parameters specified in part 7.3 (quantitative variables). These analyses will be performed at Day 8, Day 35 and Day 84 on both worst and contralateral eye.

Change from baseline in Van Bijsterveld total score at D8, D35 and D84 for both worst and contralateral eye will be analysed using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

*Assessment recorded for each eye will be analysed for the worst eye and the contralateral eye.

- DEQ-5 total score

Each question (1a, 1b, 2a, 2b and 3) will be presented, by treatment group, by frequency and percentage at each time point (Selection visit, D35 and D84). Total score and change from baseline will be tabulated, by treatment group. These analyses will be performed at Day 35 and Day 84.

Change from baseline in DEQ-5 total score at D35 and D84 will be analysed using an ANCOVA model, constructed using main effects of investigation product and baseline score as

covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

- OSDI (Ocular Surface Disease Index) total score

Each question (from Q1 to Q12) will be presented, by treatment group, by frequency and percentage at each time point (D1, D8, D35 and D84). Total score and change from baseline will be tabulated, by treatment group. These analyses will be performed at Day 8, Day 35 and Day 84.

Change from baseline in OSDI total score will be analysed at D8, D35 and D84 using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

Moreover, at each time point, OSDI total score will be presented, by treatment group, by frequency and percentage with the following modalities: Normal ([0-13[), Mild ([13-23[), Moderate ([23-33[) and Severe ([33-100]) and Cochran-Mantel-Haenszel (CMH) test will be performed for D35 and D84.

- Schirmer Test result* (without anaesthesia)

Schirmer test results at each time point (D1, D8, D35 and D84) and change from baseline will be tabulated, by treatment group. These analyses will be performed at Day 1, Day 8, Day 35 and Day 84 on both worst and contralateral eye.

Change from baseline in Schirmer Test result will be analysed at D8, D35 and D84 on both worst and contralateral eye using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

*Assessment recorded for each eye will be analysed for the worst eye and the contralateral eye.

- TBUT* (Tear Break-Up Time)

Each measure of TBUT will be presented, by treatment group, by frequency and percentage at each time point. Mean TBUT at each time point (D1, D8, D35 and D84) and change from baseline will be tabulated, by treatment group for both worst and contralateral eye. These analyses will be performed at Day 8, Day 35 and Day 84.

Change from baseline in mean TBUT will be analysed at D8, D35 and D84 on both worst and contralateral eye using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

- Conjunctival hyperaemia* using McMonnies photographic scale

Score of Conjunctival hyperaemia will be tabulated, by treatment group, at each time point

(D1, D8, D35 and D84) using frequency and percentage. Treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test based on modified ridit scores (using SCORES=MODRIDIT option in FREQ procedure), stratified by the baseline value.

*Assessment recorded for each eye will be analysed for the worst eye and the contralateral eye.

- Dry eye symptoms

Each Dry Eye symptom at Day 8, Day 35 and Day 84 will be compared between treatment group using percentage of patient with an improvement, a stability or a degradation from baseline using a Cochran-Mantel-Haenszel (CMH) test.

Total score and change from baseline will be tabulated, by treatment group. These analyses will be performed at Day 8, Day 35 and Day 84.

Change from baseline in Dry Eye Symptoms total score will be analysed at D8, D35 and D84 using an ANCOVA model, constructed using main effects of investigation product and baseline score as covariate. The LS ("adjusted") means for each treatment arm and estimates of the difference between groups (T2259 – Vismed® Multi) will be presented along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

- Performance assessment

Performance assessment by the investigator will be described by treatment group at Day 35 and Day 84 in 4 classes. An additional description will be provided in 2 classes (Very satisfactory or satisfactory, not very satisfactory or unsatisfactory). Comparison between groups on performance assessment in 4 classes will be performed using a Cochran-Mantel-Haenszel (CMH) test.

For OSI score, only listing will be provided with all corresponding items CRF.

For HLA-DR, quantification (AUF) and percentage will be presented on the whole population. Added analysis will be performed on patients with severe dry eye (OSDI>33 and/or Corneal Fluorescein Staining ≥ 3 at the baseline visit).

6.8 Safety Analysis

Safety endpoints and adverse events analysis will be provided in the Safety population by treatment group as received.

6.8.1 Safety endpoints

- Descriptive tables will be produced by frequency and percentage, for the presence of each ocular unusual sensation UPON INSTILLATION at least one time during the study (for each ocular unusual sensation UPON INSTILLATION)
- Descriptive tables will be produced by frequency and percentage, for each ocular unusual sensation UPON INSTILLATION and by mean (SD) for the total score for the 6 predefined symptoms at Day 8, Day 35 and Day 84.
- The total score for the 6 predefined symptoms will be compared between treatment groups using Student T-test, if data have normal distribution. If it is not the case, Mann-Whitney Wilcoxon test will be used.

Note: For the analysis of ocular unusual sensation UPON INSTILLATION, usual severity, usual duration and frequency will be set to 0 if the patient felt no ocular unusual sensation upon instillation or if the severity is equal to 0 (absent).

- Far best-corrected visual acuity (in logMAR) at Selection visit, Day 35 and Day 84 will be described by mean (SD) for the worst eye and for the contralateral eye. The frequency distribution will be also presented in /10 (1/10, 2/10 to 10/10, >10/10);

- Tolerance assessment by the investigator and by the patient at Day 35 and Day 84 will be described in 4 classes and in 2 classes (Very satisfactory or satisfactory, not very satisfactory or unsatisfactory). The treatment groups for 4 classes description will be compared using a Cochran-Mantel-Haenszel (CMH) test.

6.8.2 Adverse events

The adverse events were coded using the MedDRA dictionary version 22.0.

Treatment-emergent AEs (TEAEs) will be defined as AEs with onset date on or after the first day of the IMD instillation. If the AE onset date is not available, AEs will be considered as TEAEs by default.

Ocular and systemic AEs will be analysed separately on the basis of the localisation as recorded by the investigator in the CRF, i.e., localisation = Right eye, Left eye or Both eyes for ocular TEAEs, and localisation = Other for non-ocular TEAEs.

The number and percentage of patients experiencing at least one TEAE will be provided by treatment group, overall by MedDRA primary SOC and PT, for the following categories of adverse events:

- All TEAEs;
- Non-serious TEAEs;
- Treatment related TEAEs (i.e. related or missing relationship with the IMD);
- Serious TEAEs;
- TEAEs leading to medical device withdrawal.
- TEAEs by severity
- TEAEs by relationship with the IMD

Note: Results will be provided by descending frequency (for SOCs and for PTs within SOC, for the whole population analysed).

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

- Treatment group,

- Patient's identifier,
- Worse eye (right eye / left eye)
- Dry eye aetiology
- Gender,
- Age at baseline (Day 1),
- Diagnosis (verbatim),
- SOC,
- PT,
- Localisation,
- Date / time of occurence,
- Time to occurence (days) from the date of the first IMD instillation,
- Treatment-emergence
- Date / time of recovery / date of death, if any,
- Duration (days),
- Outcome,
- Frequency and details,
- Severity,
- Action taken regarding the IMD,
- Requirement for therapy adjustment / modification,
- Requirement for surgical / medical procedure,
- Seriousness,
- Relationship with the IMD in the investigator's opinion,
- Relationship with protocol procedure.

Listings will be sorted by treatment group, patient's identifier and date of onset.

The Individual data listing will present all CRF items and calculated variables as TEAE (Yes/No), time between first instillation of the study and the start date, time between first instillation and stop date, duration of the adverse event.

Listing of Deaths, Other Serious adverse events, discontinuations due to adverse events and other adverse events of special interest will be also provided for narratives.

Discontinuations due to adverse events include drug related AE leading to premature IMP drug OR study withdrawal (i.e. drug related AE with action taken = drug withdrawn OR End of study with premature discontinuation due to this AE) will be listed.

Patient data listings of COVID-19 AEs (PT: COVID-19, Coronavirus infection) will also be produced.

Individual patient data listings of non-emergent AEs will be performed on the SAF population, separately for ocular and systemic AEs.

A excel file with relevant information will also be performed for the CSR narrative.

6.8.3 Device deficiencies

Not applicable.

7 REPORTING CONVENTIONS

7.1 Software used

Statistical analysis will be made using SAS® GUIDE software (version 9.4). Tables results will be computed with SAS® GUIDE software (version 9.4). Figures will be created using Microsoft® Excel or SAS®GUIDE version 9.4.

7.2 General considerations

All p-values will be rounded to 3 decimal places. If a rounded p-value is 0.000 (i.e., the actual p-value is less than 0.0005), then this will be presented as a p-value of "<0.001".
All date fields will be presented in a format of ddmmmyyyy (e.g., 01Jan2004) in the listings.

7.3 Statistical summary conventions

For tables, sample sizes for each treatment group will be presented as total in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values.
Summaries for categorical variables will include only categories that patients had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, N missing, mean, SD, median, Q1-Q3, minimum-maximum and 95%CI. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

7.4 Examples of tables, listings and figures

7.4.1 Quantitative variables

Table xx: Description of quantitative variables

		T2259 N=xxx	Vismed N=xxx	Total N=xxx	p-value
Variable 1	**N**	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	x.xxxx
	Median	xx.x	xx.x	xx.x	
	95%CI	[xx.xx ; xx.xx]	[xx.xx ; xx.xx]	[xx.xx ; xx.xx]	
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	
	Min. ; Max.	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	
	Missing	x	x	x	
Variable 2	**N**	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	x.xxxx

	T2259 N=xxx	Vismed N=xxx	Total N=xxx	p-value
Median	xx.x	xx.x	xx.x	
95%CI	[xx.xx ; xx.xx]	[xx.xx ; xx.xx]	[xx.xx ; xx.xx]	
Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	
Min. ; Max.	xx.xx ; xx.x	xx.xx ; xx.x	xx.xx ; xx.x	
Missing	x	x	x	

Total column will be presented only for patients' disposition and for baseline characteristics.

7.4.2 Qualitative variables

Table xx: Description of qualitative variables

		T2259 N=xxx		Vismed N=xxx		p-value
		N (%)	**95%CI**	**N (%)**	**95%CI**	
Variable 1	**N**	x		x		
	Missing	x		x		
	Modality 1	xx (xx.x%)	[xx.x ; xx.x]	xx (xx.x%)	[xx.x ; xx.x]	x.xxx
	Modality 2	xx (xx.x%)	[xx.x ; xx.x]	xx (xx.x%)	[xx.x ; xx.x]	
Variable 2	**N**	x		x		
	Missing	x		x		
	Modality 1	xx (xx.x%)	[xx.x ; xx.x]	xx (xx.x%)	[xx.x ; xx.x]	x.xxx
	Modality 2	xx (xx.x%)	[xx.x ; xx.x]	xx (xx.x%)	[xx.x ; xx.x]	

Table xx: Number (%) of patients selected/not selected and reasons in case of non-selection – All screened patients

		Total N=XX
Selected patient	N	X
	No	X_1 (XX.X%)
	Yes	X (XX.X%)
Reason of non-selection	N	X_1
	Reason 1	X (XX.X%)
	Reason 2	X (XX.X%)
	…	
	Reason n	X (XX.X%)

Table xx: Number (%) of patients at each visit and type of last visit – Randomised patients

		T2259 N=xxx	Vismed N=xxx	Total N=XX
Selection visit performed	N	X	X	X
	No	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Yes	X (XX.X%)	X (XX.X%)	X (XX.X%)
D8 visit performed	N	X	X	X
	No	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Yes	X (XX.X%)	X (XX.X%)	X (XX.X%)

D35 visit performed	N	X	X	X
	No	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Yes	X (XX.X%)	X (XX.X%)	X (XX.X%)
D84 visit performed	N	X	X	X
	No	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Yes	X_1 (XX.X%)	X_1 (XX.X%)	X_1 (XX.X%)
Type of D84 visit	N	X_1	X_1	X_1
	D84 visit	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Withdrawal visit	X (XX.X%)	X (XX.X%)	X (XX.X%)

Table xx: Number (%) of patients in each populations and reasons of exclusion – Randomised patients

		T2259 N=xxx	Vismed N=xxx	Total N=XX
Safety population	N	X	X	X
	No	X_0 (XX.X%)	X_0 (XX.X%)	X_0 (XX.X%)
	Yes	X_1 (XX.X%)	X_1 (XX.X%)	X_1 (XX.X%)
Reason of exclusion of Safety population	N	X_0	X_0	X_0
	Reason 1	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Reason 2	X (XX.X%)	X (XX.X%)	X (XX.X%)
	…			
	Reason n	X (XX.X%)	X (XX.X%)	X (XX.X%)
FAS population	N	X_1	X_1	X_1
	No	X_2 (XX.X%)	X_2 (XX.X%)	X_2 (XX.X%)
	Yes	X_3 (XX.X%)	X_3 (XX.X%)	X_3 (XX.X%)
Reason of exclusion of FAS population	N	X_2	X_2	X_2
	Reason 1	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Reason 2	X (XX.X%)	X (XX.X%)	X (XX.X%)
	…			
	Reason n	X (XX.X%)	X (XX.X%)	X (XX.X%)
PP population	N	X_3	X_3	X_3
	No	X_4 (XX.X%)	X_4 (XX.X%)	X_4 (XX.X%)
	Yes	X_5 (XX.X%)	X_5 (XX.X%)	X_5 (XX.X%)

Reason of exclusion of PP population	N	X_4	X_4	X_4
	Reason 1	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Reason 2	X (XX.X%)	X (XX.X%)	X (XX.X%)
	…			
	Reason n	X (XX.X%)	X (XX.X%)	X (XX.X%)

7.4.3 Protocol deviations

Table xx: Protocol deviations – XX population

	T2259 N=xxx	**Vismed N=xxx**	**Total N=xxx**
At least one major deviation			
Deviation 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Deviation 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…			
At least one minor deviation*			
Deviation 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Deviation 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…			
Only minor deviation			
Deviation 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Deviation 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…			

* includes major deviations

7.4.4 Adverse Events

Table xx: Overview of (*) TEAEs – Safety population

	T2259 N=xxx	**Vismed N=xxx**
Any TEAE	xx (xx.x %)	xx (xx.x %)
Any serious TEAE	xx (xx.x %)	xx (xx.x %)
Any IMP-related TEAE	xx (xx.x %)	xx (xx.x %)
Any TEAE leading to premature IMD withdrawal	xx (xx.x %)	xx (xx.x %)

Programming notes: replace (*) by “ocular” and “systemic”

Table xx: AEs description by SOC and PT

SOC and PT	**T2259 N=xxx**			**Vismed N=xxx**		
	AE (1)	**n (2)**	**% (3)**	**AE (1)**	**n (2)**	**% (3)**
Patients with at least one (*)	xx	xx	xx.x	xx	xx	xx.x

SOC and PT	T2259 N=xxx			Vismed N=xxx		
	AE (1)	n (2)	% (3)	AE (1)	n (2)	% (3)
SOC 1	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 1	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 2	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x
SOC 2	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 1	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 2	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x

(1) Number of AEs: each AE is counted only once per SOC/PT
(2) Number of subjects with at least one AE: each patient is counted only once per SOC/PT
(3) % of subjects with at least one AE
MedDRA version 22.0
SOC=System Organ Class, PT=Preferred Term, AE=Adverse Event.

Programming notes: replace (*) by TEAE, ADE or SAD, depending on the table; when needed, update abbreviations.

Table xx: All TEAEs by SOC, PT and severity (XX treatment group) – Safety population

	TEATMENT GROUP (LT2259 or VisMed) N=XX								
	Mild			Moderate			Severe		
SOC and PT	AE (1)	n (2)	% (3)	AE (1)	n (2)	% (3)	AE (1)	n (2)	% (3)
Patients with at least one (*)	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x

(1) Number of AEs: each AE is counted only once per SOC/PT
(2) Number of subjects with at least one AE: each patient is counted only once per SOC/PT
(3) % of subjects with at least one AE
MedDRA version 22.0
SOC=System Organ Class, PT=Preferred Term, AE=Adverse Event.
Programming notes: replace (*) by TEAE, ADE or SAD, depending on the table; when needed, update abbreviations;

Table xx: All TEAEs by SOC, PT and relationship (XX treatment group) – Safety population

	TEATMENT GROUP (LT2259 or VisMed) N=XX					
SOC and PT	Not related to IMD			Related to IMD		
	AE	n	%	AE	n	%

	(1)	(2)	(3)	(1)	(2)	(3)
TOTAL	xx	xx	xx.x	xx	xx	xx.x
SOC 1	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 1	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 2	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x
SOC 2	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 1	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 2	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x

8 TABLES, LISTING AND FIGURES

8.1 Planned tables

Part 6.1 and 6.2: Disposition of patients

Table 1.1: First date and last date of selection visit, inclusion visit and last visit – All screened patients
Table 1.2: Number (%) of patients selected/not selected and reasons in case of non-selection – All screened patients
Table 1.3: Number (%) of patients who attended inclusion visit, number of patients included/not included and reasons in case of non-inclusion – Selected patients
Table 1.4: Number (%) of patients randomised/not randomised and reasons in case of non-randomisation – Included patients
Table 1.5: Number (%) of patients at each visit and type of last visit – Randomised patients
Table 1.6a: Number (%) of patients who completed the study and reasons in case of withdrawal – Randomised patients
Table 1.6b: Number (%) of patients who completed the study and reasons in case of withdrawal by possible impact of COVID-19 – SAF population
Table 1.6c: Number (%) of patients who completed the study and reasons in case of withdrawal by possible impact of COVID-19 – FAS population
Table 1.7a: Number (%) of patients in each population and reasons of exclusion – Randomised patients
Table 1.7b: Number (%) of patients in each population and reasons of exclusion by possible impact of COVID-19 – Randomised patients
Table 1.8a: Number (%) of patients in each country and site – FAS population
Table 1.8b: Number (%) of patients in each country and site by possible impact of COVID-19 – FAS population
Table 1.8c: Number (%) of patients in each country and site – SAF population
Table 1.8d: Number (%) of patients in each country and site by possible impact of COVID-19 – SAF population
Table 1.9: Time since inclusion for each visit – FAS population
Table 1.10: Study duration – FAS population
Table 1.11a: Protocol deviations – FAS population
Table 1.11b: Protocol deviations by possible impact of COVID-19 – FAS patient

Part 6.3: Demographic and baseline characteristics

Table 2.1a: Demographic characteristics – PP population
Table 2.1b: Demographic characteristics – FAS population
Table 2.1c: Demographic characteristics by possible impact of COVID-19 – SAF population
Table 2.1d: Demographic characteristics by possible impact of COVID-19 – FAS population
Table 2.2a: History of Dry Eye– PP population
Table 2.2b: History of Dry Eye– FAS population
Table 2.3a: Ocular medical history other than the studied disease by SOC and PT – PP population
Table 2.3b: Ocular medical history other than the studied disease by SOC and PT – PP population
Table 2.4a: Ocular medical surgery other than the studied disease by SOC and PT – PP population
Table 2.4b: Ocular medical surgery other than the studied disease by SOC and PT – FAS populations
Table 2.5a: Systemic medical history other than the studied disease by SOC and PT – PP populations
Table 2.5b: Systemic medical history other than the studied disease by SOC and PT – FAS populations
Table 2.6a: Systemic medical surgery other than the studied disease by SOC and PT – PP population
Table 2.6b: Systemic medical surgery other than the studied disease by SOC and PT – FAS population

Part 6.5: Previous and Concomitant Medications

Table 3.1a: Previous ocular treatments by ATC level 2 and 4 – PP population
Table 3.1b: Previous ocular treatments (by ATC level 2 and 4) – FAS population
Table 3.2a: Concomitant ocular treatments (by ATC level 2 and 4) – PP population
Table 3.2b: Concomitant ocular treatments (by ATC level 2 and 4) – FAS population

Table 3.3a: Previous non-ocular treatments (by ATC level 2 and 4) – PP population
Table 3.3b: Previous non-ocular treatments (by ATC level 2 and 4) – FAS population
Table 3.4a: Concomitant non-ocular treatments (by ATC level 2 and 4) – PP population
Table 3.4b: Concomitant non-ocular treatments (by ATC level 2 and 4) – FAS population

Table 3.5a: Post-study treatments (by ATC level 2 and 4) – PP population
Table 3.5b: Post-study treatments (by ATC level 2 and 4) – FAS population

Part 6.6: Treatment exposure during the run-in period and IMD

Table 4.1a: Treatment with Hyderabak duration in run-in period – Safety population
Table 4.1b: Treatment with Hyderabak duration in run-in period – PP population
Table 4.1c: Treatment with Hyderabak duration in run-in period – FAS population

Table 4.2a: Time between last instillation of Hydrabak and inclusion visit date – Safety population
Table 4.2b: Time between last instillation of Hydrabak and inclusion visit date – PP population
Table 4.2c: Time between last instillation of Hydrabak and inclusion visit date – FAS population
Table 4.3a: Respect of dosage for Hydrabak – Safety population
Table 4.3b: Respect of dosage for Hydrabak – PP population
Table 4.3c: Respect of dosage for Hydrabak – FAS population
Table 4.4a: Study treatment duration – Safety population
Table 4.4b: Study treatment duration – PP population
Table 4.4c: Study treatment duration – FAS population
Table 4.5a: Mean daily dose regimen – Safety population
Table 4.5b: Mean daily dose regimen – PP population
Table 4.5c: Mean daily dose regimen – FAS population

Part 6.7: Performance analysis

Primary performance endpoint:

Table 5.1a: Oxford total score at each timepoint and change from baseline – Worst eye – PP population
Table 5.1b: Oxford total score at each timepoint and change from baseline – Worst eye – FAS population
Table 5.1c: Oxford total score at each timepoint and change from baseline – Worst eye – with LOCF imputation –– FAS population
Table 5.2a: Oxford grade by panel at each timepoint and change from baseline – Worst eye – PP population
Table 5.2b: Oxford grade by panel at each timepoint and change from baseline – Worst eye – FAS population
Table 5.2c: Oxford grade by panel at each timepoint and change from baseline – Worst eye – with LOCF imputation –– FAS population
Table 5.3a: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – (with country and country by treatment interaction) – PP population
Table 5.3b: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – (with country and country by treatment interaction) – FAS population
Table 5.3c: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – (with country and country by treatment interaction) – with LOCF imputation –– FAS population
Table 5.4a: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye –– PP population
Table 5.4b: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – as observed – FAS population
Table 5.4c: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – with LOCF imputation –– FAS population
Table 5.5a: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – by possible impact of COVID-19 pandemic – PP population

Table 5.5b: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – by possible impact of COVID-19 pandemic – FAS population
Table 5.5c: Results of ANCOVA analysis in change from baseline in Oxford total score at D35 – Worst eye – by possible impact of COVID-19 pandemic – with LOCF imputation –– FAS population
Table 5.6a: Results of MMRM analysis in change from baseline in Oxford total score at D35 – Worst eye – PP population
Table 5.6b: Results of MMRM analysis in change from baseline in Oxford total score at D35 – Worst eye – FAS population
Table 5.6c: Results of MMRM analysis in change from baseline in Oxford total score at D35 – Worst eye – with LOCF imputation –– FAS population

Secondary performance endpoints:

Table 5.7a: Results of ANCOVA analysis in change from baseline in Oxford total score at D8 and D84 – Worst eye – PP population
Table 5.7b: Results of ANCOVA analysis in change from baseline in Oxford total score at D8 and D84 – Worst eye – FAS population

Table 5.8a: Oxford total score at each timepoint and change from baseline – Contralateral eye – PP population
Table 5.8b: Oxford total score at each timepoint and change from baseline – Contralateral eye – FAS population
Table 5.9a: Oxford grade by panel at each timepoint and change from baseline – Contralateral eye – PP population
Table 5.9b: Oxford grade by panel at each timepoint and change from baseline – Contralateral eye – FAS population

Table 5.10a: Results of ANCOVA analysis in change from baseline in Oxford total score at D8, D35 and D84 – Contralateral eye – PP population
Table 5.10b: Results of ANCOVA analysis in change from baseline in Oxford total score at D8, D35 and D84 – Contralateral eye – FAS population

Table 5.11a: Van Bijsterveld items at each timepoint – Worst eye – PP population
Table 5.11b: Van Bijsterveld items at each timepoint – Worst eye – FAS population

Table 5.12a: Van Bijsterveld total score at each timepoint and change from baseline – Worst eye – PP population
Table 5.12b: Van Bijsterveld total score at each timepoint and change from baseline – Worst eye – FAS population

Table 5.13a: Van Bijsterveld – Results of ANCOVA analysis in change from baseline in Van Bijsterveld total score at D8, D35 and D84 – Worst eye – PP population
Table 5.13b: Van Bijsterveld – Results of ANCOVA analysis in change from baseline in Van Bijsterveld total score at D8, D35 and D84 – Worst eye – FAS population

Table 5.14a: Van Bijsterveld items at each timepoint – Contralateral eye – PP population
Table 5.14b: Van Bijsterveld items at each timepoint – Contralateral eye – FAS population

Table 5.15a: Van Bijsterveld total score at each timepoint and change from baseline – Contralateral eye – PP population
Table 5.15b: Van Bijsterveld total score at each timepoint and change from baseline – Contralateral eye – FAS population

Table 5.16a: Van Bijsterveld – Results of ANCOVA analysis in change from baseline in Van Bijsterveld total score at D8, D35 and D84 – Contralateral eye – PP population
Table 5.16b: Van Bijsterveld – Results of ANCOVA analysis in change from baseline in Van Bijsterveld total score D8, D35 and D84 – Contralateral eye – FAS population

Table 5.17a: DEQ-5 items at each timepoint – PP population
Table 5.17b: DEQ-5 items at each timepoint – FAS population
Table 5.18a: DEQ-5 total score at each timepoint and change from baseline – PP population
Table 5.18b: DEQ-5 total score at each timepoint and change from baseline – FAS population
Table 5.19a: DEQ-5 – Results of ANCOVA analysis in change from baseline in DEQ-5 total score at D35 and D84 – PP population
Table 5.19b: DEQ-5 – Results of ANCOVA analysis in change from baseline in DEQ-5 total score at D35 and D84 – FAS population

Table 5.20a: OSDI items at each timepoint – PP population
Table 5.20b: OSDI items at each timepoint – FAS population

Table 5.21a: OSDI total score at each timepoint and change from baseline – PP population
Table 5.21b: OSDI total score at each timepoint and change from baseline – FAS population

Table 2.22a: OSDI – Results of ANCOVA analysis in change from baseline in OSDI total score at D8, D35 and D84 – PP population
Table 5.22b: OSDI – Results of ANCOVA analysis in change from baseline in OSDI total score at D8, D35 and D84 – FAS population

Table 5.23a: OSDI total score in classes at each timepoint – PP population
Table 5.23b: OSDI total score in classes at each timepoint – FAS population

Table 5.24a: Schirmer test results at each timepoint and change from baseline – Worst eye – PP population
Table 5.24b: Schirmer test results at each timepoint and change from baseline – Worst eye – FAS population

Table 5.25a: Schirmer test – Results of ANCOVA analysis in change from baseline in Schirmer test at D8, D35 and D84 – Worst eye – PP population
Table 5.25b: Schirmer test – Results of ANCOVA analysis in change from baseline in Schirmer test at D8, D35 and D84 – Worst eye – FAS population

Table 5.26a: Schirmer test results at each timepoint and change from baseline – Contralateral eye – PP population
Table 5.26b: Schirmer test results at each timepoint and change from baseline – Contralateral eye – FAS population

Table 5.27a: Schirmer test – Results of ANCOVA analysis in change from baseline in Schirmer test at D8, D35 and D84 – Contralateral eye – PP population
Table 5.27b: Schirmer test – Results of ANCOVA analysis in change from baseline in Schirmer test at D8, D35 and D84 – Contralateral eye – FAS population

Table 5.28a: Measurements of TBUT at each timepoint – Worst eye – PP population
Table 5.28b: Measurements of TBUT at each timepoint – Worst eye – FAS population

Table 5.29a: Mean TBUT at each timepoint and change from baseline – Worst eye – PP population
Table 5.29b: Mean TBUT at each timepoint and change from baseline – Worst eye – FAS population

Table 5.30a: Mean TBUT – Results of ANCOVA analysis in change from baseline in TBUT at D8, D35 and D84 – Worst eye – PP population
Table 5.30b: Mean TBUT – Results of ANCOVA analysis in change from baseline in TBUT at D8, D35 and D84 – Worst eye – FAS population

Table 5.31a: Measurements of TBUT at each timepoint – Contralateral eye – PP population
Table 5.31b: Measurements of TBUT at each timepoint – Contralateral eye – FAS population

Table 5.32a: Mean TBUT at each timepoint and change from baseline – Contralateral eye – PP population
Table 5.32b: Mean TBUT at each timepoint and change from baseline – Contralateral eye – FAS population

Table 5.33a: Mean TBUT – Results of ANCOVA analysis in change from baseline in mean TBUT at D8, D35 and D84 – Contralateral eye – PP population
Table 5.33b: Mean TBUT – Results of ANCOVA analysis in change from baseline in mean TBUT at D8, D35 and D84 – Contralateral eye – FAS population

Table 5.34a: Conjunctival hyperaemia at each timepoint – Worst eye – PP population
Table 5.34b: Conjunctival hyperaemia at each timepoint – Worst eye – FAS population

Table 5.35a: Conjunctival hyperaemia at each time point – Contralateral eye – PP population
Table 5.35b: Conjunctival hyperaemia at each time point – Contralateral eye – FAS population

Table 5.36a: Dry eye symptoms at each timepoint – PP population
Table 5.36b: Dry eye symptoms at each timepoint – FAS population

Table 5.37a: Dry eye symptoms total score at each timepoint and change from baseline – PP population

Table 5.37b: Dry eye symptoms total score at each timepoint and change from baseline – FAS population

Table 5.38a: Dry eye symptoms – Results of ANCOVA analysis in change from baseline in dry eye symptoms total score at D8, D35 and D84 – PP population
Table 5.38b: Dry eye symptoms – Results of ANCOVA analysis in change from baseline in dry eye symptoms total score at D8, D35 and D84 – FAS population

Table 5.39a: Performance assessment by the investigator at each time point – PP population
Table 5.39b: Performance assessment by the investigator at each time point – FAS population

Table 5.40a: Quantification (AUF) and percentage of HLA-DR at each timepoint – PP population
Table 5.40b: Quantification (AUF) and percentage of HLA-DR at each timepoint – FAS population

Table 5.41a: Quantification (AUF) and percentage of HLA-DR in patients with severe dry eye at D84 – PP population
Table 5.41b: Quantification (AUF) and percentage of HLA-DR in patients with severe dry eye at D84 – FAS population

Part 6.8: Safety analysis

Safety endpoints:

Table 6.1: Ocular unusual sensation UPON INSTILLATION at least one time during the study– Safety population
Table 6.2: Ocular unusual sensation UPON INSTILLATION at each timepoint – Safety population
Table 6.3: Ocular unusual sensation UPON INSTILLATION total score at each timepoint – Safety population

Table 6.4a: Far BCVA (in logMAR) at each timepoint – Worst eye – Safety population
Table 6.4b: Far BCVA (/10) at each timepoint – Worst eye – Safety population

Table 6.5a: Far BCVA (in logMAR) at each timepoint – Contralateral eye – Safety population
Table 6.5b: Far BCVA (/10) at each timepoint – Contralateral eye – Safety population

Table 6.6a: Tolerance assessment by the investigator at each timepoint – Safety population
Table 6.6b: Tolerance assessment by the patient at each timepoint – Safety population

Adverse events:

Table 6.7: Overview of ocular TEAEs – Safety population
Table 6.8: Overview of systemic TEAEs – Safety population
Table 6.9: Ocular TEAEs by SOC and PT – Safety population
Table 6.10: Non-ocular TEAEs by SOC and PT – Safety population

Table 6.11: Ocular non-serious TEAEs by SOC and PT – Safety population
Table 6.12: Systemic non-serious TEAEs by SOC and PT – Safety population
Table 6.13: Ocular treatment related TEAEs by SOC and PT – Safety Population
Table 6.14: Systemic treatment related TEAEs by SOC and PT – Safety Population
Table 6.15: Serious ocular TEAEs by SOC and PT – Safety population
Table 6.16: Serious systemic TEAEs by SOC and PT – Safety population
Table 6.17: Ocular TEAEs leading to medical device withdrawal by SOC and PT – Safety population
Table 6.18: Systemic TEAEs leading to medical device withdrawal by SOC and PT – Safety population
Table 6.19a: Ocular TEAEs by SOC, PT and severity (LT2259) – Safety population
Table 6.19b: Ocular TEAEs by SOC, PT and severity (Vismed) – Safety population
Table 6.20a: Systemic TEAEs by SOC, PT and severity (LT2259) – Safety population
Table 6.20b: Systemic TEAEs by SOC, PT and severity (Vismed) – Safety population
Table 6.21a: Ocular TEAEs by SOC, PT and relationship with the investigational medical device (LT2259) – Safety population
Table 6.21b: Ocular TEAEs by SOC, PT and relationship with the investigational medical device (Vismed) – Safety population
Table 6.22a: Systemic TEAEs by SOC, PT and relationship with the investigational medical device (LT2259) – Safety population
Table 6.22b: Systemic TEAEs by SOC, PT and relationship with the investigational medical device (Vismed) – Safety population

8.2 Planned listings

Listings 3 and 4 will include PP and FAS populations (as variable) and listing 5 will include FAS population.

Part 6.2:

Listing 1: Non-selected patients, non-included patients and early withdrawals – All screened patients
Listing 2: Protocol deviations – FAS population

Part 6.3:

Listing 3: Other aetiology of Dry Eye – Safety population

Part 6.5:

Listing 4: Previous and concomitant treatments – Safety population

Part 6.6:

Listing 5: Daily dose regimen different from 2 to 4 instillations/day – Safety population

Part 6.7:

Listing 6: OSI score – FAS population

Part 6.8:

Listing 7: Listing of individual data of overall systemic TEAEs – Safety population
Listing 8: Listing of individual data of overall ocular TEAEs – Safety population
Listing 9: Listing of individual data of overall systemic SAEs – Safety population
Listing 10: Listing of individual data of overall ocular SAEs – Safety population
Listing 11: Listing of individual data of overall systemic SADEs – Safety population
Listing 12: Listing of individual data of overall ocular SADEs – Safety population
Listing 13: Listing of individual data of non-emergent systemic AEs – Enrolled population
Listing 14: Listing of individual data of non-emergent ocular AEs – Enrolled population
Listing 15: Listing of COVID-19 AEs – Enrolled population

8.3 Planned figures

Figure 1: Flowchart

9 REFERENCES

NA.

10 APPENDICES

10.1 Appendix 1: Level of validation for analyses programming

This chapter documents the validation of the statistical analysis programs. The level of validation is defined with reference to the procedure "Programming of the statistical analysis". All the analyses and programs have a default validation level "Basic + NC".
Analysis below have a CR validation level:

Analyses	Validation level	Programs
Randomisation (when unblinding)	CR	FICH
Populations	CR	FICH
Derived data	CR	FICH
Primary efficacy endpoint (section 7.6.1)	CR	ANA_PRINC
Ocular unusual sensation UPON INSTILLATION	CR	ANA_SAFE
Adverse events	CR	ANA_SAFE

Key:
Basic = Corresponds to the self-check of the programming by any person who is required to program, as well as the checking of derived variables (see self-check frame)
NC (non-critical) = The tables, listings and figures compiled in a single document shall be verified by one qualified person other than the program developer with the support of the CRF and SAP for the study.
CR (critical) = A double programming and a comparison of the results should be performed by one qualified person other than the program developer.