1 GENERALITIES

CLINICAL INVESTIGATION PLAN

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

Investigation No. LT2259-001

Sponsor

Laboratoires Théa

12, rue Louis Blériot

63017 Clermont-Ferrand Cedex 2, France

Phone number: +33 4 73 98 14 36

Date of the initial Clinical Investigation Plan: 03/01/2020
Version of the initial Clinical Investigation Plan: Version

Amendments	
No.	Date
1	
2	
3	

LABORATOIRES THÉA

Clinical Investigation Plan (CIP) No.: LT2259-001

Investigational Medical Device (IMD): T2259 or Vismed® Multi

Intended purpose: to demonstrate the performance of T2259 versus Vismed® Multi as non-inferiority

International Coordinating Investigator: Professor Christophe BAUDOUIN

Medical Operations Director: Doctor Beatriz ROMERO RUBIOLS

DECLARATION OF THE SPONSOR AND OF THE COORDINATING INVESTIGATOR

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

The information contained in this CIP is consistent with:

- The current risk-benefit evaluation of the Medical Device;
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, Good Clinical Practice GCP and ISO14155.

The Investigator will be provided with details of any significant or new findings, including adverse events, relating to treatment with the IMD.

INTERNATIONAL COORDINATING INVESTIGATOR

Professor Christophe BAUDOUIN _____ _____
First Name - Name *date* *signature*

SPONSOR: LABORATOIRES THÉA

Medical Operations Director
Beatriz Romero Rubiols _____ _____
First Name - Name *date* *signature*

Ophthalmology Expert Physician
Dariusz Rokicki _____ _____
First Name - Name *date* *signature*

Clinical Trials Manager
Lydia Bresson _____ _____
First Name - Name *date* *signature*

Clinical applications and Biometrics Manager
Sylvie Nisslé _____ _____
First Name - Name *date* *signature*

INVESTIGATOR SIGNATURE PAGE

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

The signature below:

- Confirms my agreement to conduct the investigation in compliance with ISO 14155, Good Clinical Practices (GCP), applicable regulatory, and the CIP requirement(s);
- Confirms my agreement to comply with procedures for data recording/reporting;
- Confirms my agreement to permit monitoring, auditing, and regulatory inspection;
- Confirms my agreement to retain the essential documents of this investigation in the Investigator files until Laboratoires Théa informs me that these documents are no longer needed (e.g. over 15 years);
- Ensure that all people assisting with the investigation are adequately informed about the CIP, the IMD(s) and their trial-related duties and functions;
- Confirms that I have read this CIP and that I agree to comply with all parts or items.

All information regarding this CIP and the IMD(s) will be treated as strictly confidential.

TRIAL SITE Investigational site

Principal Investigator		
First Name - Name	*date*	*signature*

SPONSOR: LABORATOIRES THÉA
Clinical Project Leader

Marielle ESTRADE		
First Name - Name	*date*	*signature*

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CIP Synopsis

Title	**Comparison of the performance and safety of T2259 versus Vismed® Multi in dry eye patients with superficial keratitis.**
Sponsor	Laboratoires Théa
Sponsor Investigation No.	LT2259-001
International Coordinating Investigator	Prof. Christophe Baudouin
Investigation Centre(s)	This investigation is planned to be carried out at approximately 35 sites in France, in Spain, in Slovakia and in Poland.
Planned Schedule	▪ Planned initiation: October 2018 ▪ Planned last patient last visit: December 2020
Primary Investigation Objective	The primary objective of this study is to demonstrate the non-inferiority of T2259 versus Vismed® Multi in terms of performance.
Secondary Investigation Objective(s)	To evaluate the safety and performance of T2259 versus Vismed® Multi.
Primary Performance criterion	▪ Change from baseline in total ocular staining grade according to Oxford 0-15 grading scheme (corneal staining by fluorescein, nasal and temporal conjunctival staining by lissamine green) at Day 35 in the worst eye.
Secondary Performance criteria	• 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 for contralateral eye. • Change from baseline in Van Bijsterveld score* (lissamine green staining) at Day 8, Day 35 and Day 84. • Change from Day1-10/Day1-7 (selection visit) 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 Day 84.

	• 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.
Safety parameters	• Ocular symptoms 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 evaluated with a 4-level verbal scale (0=Absent, 1=Present but not disturbing, 2=Disturbing but not limiting daily activities, 3=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 using a 4-point verbal scale (Unsatisfactory, Not very satisfactory, Satisfactory, Very satisfactory) at Day 35 and Day 84. • Ocular and systemic adverse events (AE/SAE).
Statistical method	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® Multi, 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 alpha=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.

Sample size	90 randomised patients.
Investigation Design	Multicentre, randomised study, investigator-masked, 2 parallel groups (T2259 versus Vismed® Multi) of 38 evaluable patients each.
Investigation Duration	Run-in-period with preservative free artificial tears (Hydrabak®): from Day 1-10 or Day 1-7 to randomisation visit (Day 1) (one drop in each eye 3 to 6 times daily). ▪ Treatment period: 84 ± 7 days ▪ Total study duration: maximum of 101 days
Investigational Medical Device(s) (IMD)	**<u>T2259</u>** **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.
	<u>Vismed® Multi</u> **Formulation:** Sodium Hyaluronate, 0.18% **Route of administration:** Eye drops **Daily dose regimen:** One drop in each eye 2 to 4 times daily.
Investigation Visits	Day 1-10/Day 1-7 Selection visit (Visit 1) Day 1 Randomisation 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) Visits V2, V3, V4 and V5 should be performed at the same hour (±4 hours)
Inclusion Criteria *at selection visit*	1.1. Informed consent signed and dated. 1.2. Male or female aged ≥ 18 years old. 1.3. Known Dry Eye Syndrome requiring artificial tears within the last 3 months prior to study selection.
Inclusion Criteria *at Randomisation visit (Day 1)*	1.4. 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). 1.5. No ocular instillation at least 6 hours prior to the randomisation visit (Day 1). 1.6. Diagnosis of moderate to severe dry eye syndrome defined by OSDI Score ≥ 23. 1.7. 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.
Exclusion Criteria **At selection visit**	**<u>Ophthalmic Exclusion Criteria in AT LEAST ONE EYE</u>** 2.1.1. Far best-corrected visual acuity ≤ 2/10. 2.1.2. Severe blepharitis (grade 3 / 0-3 scale). 2.1.3. Ocular rosacea. 2.1.4. Severe Dry Eye associated to: - Eyelid malposition, - Corneal dystrophy, - Ocular neoplasia, - Filamentous keratitis, - Corneal neovascularisation, - Orbital radiotherapy. 2.1.5. History of ocular trauma, ocular infection or ocular inflammation within the last 3 months. 2.1.6. History of ocular allergy. 2.1.7. History of uveitis. 2.1.8. History of inflammatory corneal ulcer within the last 12 months. 2.1.9. Glaucoma, ocular hypertension requiring glaucoma treatment.
Exclusion Criteria (continued)	**<u>Systemic/non Ophthalmic Exclusion Criteria</u>** 2.2.1. Known or suspected hypersensitivity to one of the components of the Investigational Device or auxiliary products. 2.2.2. 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. 2.2.3. Allergic rhinitis active or susceptible to reactivate during the study. 2.2.4. 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). **<u>Specific Exclusion Criteria Regarding Childbearing Potential Women</u>** 2.3.1 Pregnancy or breastfeeding. 2.3.2 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. **<u>Exclusion Criteria Related to General Conditions</u>** 2.4.1. Inability of patient to understand the study procedures or to give informed consent. 2.4.2. Non-compliant patient (*e.g.*, not willing to attend a visit or completing the self-questionnaire; way of life interfering with compliance). 2.4.3. Participation in this investigation at the same time as another clinical investigation. 2.4.4. Participation in this investigation during the exclusion period of another clinical study. 2.4.5. Patient previously randomised in this study. 2.4.6. Patient being institutionalised 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. 2.4.7. Patient not covered by the government health care scheme of the country in which he/she is living. 2.4.8. Patient under guardianship/ward of court **<u>Exclusion criteria related to previous and concomitant treatments (medications/non-medicinal therapies/procedures)</u>** 2.5.1. 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 Table 1.
Schedule of Assessments	For further details, refer to the schedule of assessments as flowchart study.

Table 1 Prohibited treatments (medications/non-medicinal therapies/procedures)

<table>
<tr><td colspan="8">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 colspan="2">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 colspan="2">Run-in period</td><td>Treatment period</td></tr>
<tr><td colspan="8">Corneal surgery, ...</td></tr>
<tr><td colspan="8">Intraocular injections…….</td></tr>
<tr><td colspan="8">Other ocular surgeries (e.g. cataract, palpebral)……...
Isotretinoïde, cyclosporine, tacrolimus, sirolimus, pimecrolimus…….</td></tr>
<tr><td colspan="8">Any change in systemic medication already ongoing before selection visit……..
Permanent punctal plugs……..</td></tr>
<tr><td colspan="8">Semi-permanent or temporary punctal plugs……..</td></tr>
<tr><td colspan="8">Contact lenses……</td></tr>
<tr><td colspan="7">Any ocular medication other than Hydrabak®</td><td></td></tr>
<tr><td colspan="7"></td><td>Any ocular medication including artificial tears other than authorized medical devices</td></tr>
</table>

Table 2 Schedule of Visits and Procedures

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

ABBREVIATIONS

ADE	Adverse Device Effect
ADDE	Aqueous Deficient Dry Eye
AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
ASADE	Anticipated Serious Adverse Device Effect
AUF	Arbitrary Units of Fluorescence
BCVA	Far Best-corrected visual acuity
CIP	Clinical Investigational Plan
CMH	Cochran-Mantel-Haenszel test
e-CRF	Electronic Case Report Form
CRO	Contract Research Organisation
DED	Dry Eye Disease
DES	Dry Eye Syndrome
EDE	Evaporative Dry Eye
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HLA-DR	Human Leukocyte Antigen – antigen D Related
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IMD	Investigational Medical Device
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
LPPR	List of Products Reimbursed by French Social Security

MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
OQAS	Optical Quality Analysing System
OSI	Optical Scattering Index
OSDI	Ocular Surface Disease Index
PMS	Post-Market Surveillance
PP	Per Protocol
PT	Preferred Term
RMP	Risk Management Plan
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source data verification
SH	Sodium Hyaluronate
SOC	System Organ Class
TBUT	Tear Break-up Time
TEAE	Treatment emergent adverse events
TFT	Tear Film thickness
USADE	Unanticipated Serious Adverse Device Effect

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2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL MEDICAL DEVICE

2.1 Summary description of the investigational medical device (IMD) and its intended purpose

T2259 device is an isotonic neutral, clear and colourless solution developed to protect, hydrate and lubricate the eye. It contains Trehalose and Sodium Hyaluronate (SH).

T2259 device is packed in a multidose, white polyethylene ABAK® system bottle. The ABAK® container is a multidose eye-drop delivery system in which non-preserved solutions are entirely protected from microbial contamination by a membrane filter with very low porosity (0.2 µm). This ABAK® dispenser is already used for several currently marketed eye drops.

2.2 Manufacturing

T2259 device is manufactured by FARMILA-THEA Farmaceutici SpA, Via Fermi 50 – Settimo Milanese (MI) Italy in accordance with the European Union (EU) Good Manufacturing Practice (GMP), including the EU GMP Annex 13.

The IMD will be packaged by approved contractor in accordance with Good Manufacturing Practices (GMP).

The legal manufacturer of T2259 according to the directive 93/42 CEE is Laboratoires Théa.

The process uses techniques and equipment which the manufacturer is experienced with and which are fully controlled, since FARMILA-THEA already produces several ophthalmic preparations.

2.3 Intended purpose of the IMD in the proposed clinical investigation

T2259 eye drops are intended to protect, hydrate and lubricate in dry eye patients with superficial keratitis.

2.4 The populations and indications for which the IMD is intended

T2259 eye-drops are intended to be used in dry eye patients with superficial keratitis.

2.5 Description of the IMD

T2259 is an isotonic neutral, clear and colourless solution to protect, hydrate and lubricate the eye.

T2259 is packaged in a multidose white polyethylene ABAK® system bottle. The ABAK® container is a multidose eye-drop delivery system in which non-preserved solutions are entirely protected from microbial contamination by a membrane filter with very low porosity (0.2 µm). The dispenser is already used in several currently marketed eye drops.

The composition and function of the different ingredients of T2259 are detailed in Table 3.

The excipients of the T2259 eye-drops (trometamol, sodium chloride, hydrochloric acid and water for injections) are well-known and commonly used in ophthalmic formulations.

Table 3 Investigational medical device T2259

Names of ingredients	***Percentage formula (g/100 ml)***	***Function***	***Reference to standards***
Water for injections	**qsp 100 ml**	Vehicle	Current Eur. Ph. [0169]
Trehalose*	6.00	Lubricating, hydrating agent	Current Eur. Ph. [2297]
Sodium Hyaluronate**	0.20	Lubricating, hydrating agent	Current Eur. Ph. [1472] and Certificate of Suitability
Sodium chloride	0.15	Isotonising agent	Current Eur. Ph. [0193]
Trometamol	0.242	pH buffer	Current Eur. Ph. [1053]
Hydrochloric acid, concentrated***	ad pH 7.0	pH adjustment	Current Eur. Ph. [0002]

* The quantity of Trehalose dihydrate is adjusted as a function of its titre and water content
** The quantity of Sodium Hyaluronate is adjusted as a function of its water content
*** Used under the form of a 1N solution for pH adjustment

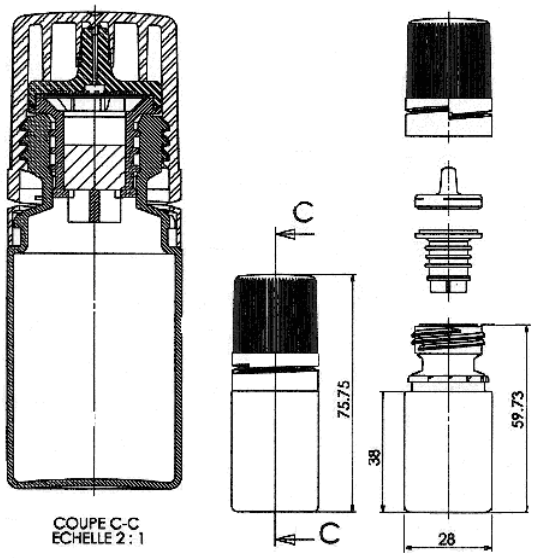
2.6 Packaging and Labeling

The originality of the product resides in its packaging suitable for preservative-free multi-dose eye-drop presentations, thus avoiding the toxic and allergenic effects of the latter on the cornea.

T2259 is presented in a bottle (Figure 1), consisting in a polyethylene white opaque bottle which has an insert in its neck. The insert is made of two parts:

- The dropper device, to which is joined an antimicrobial membrane with a pore size of 0.2 µm, which protects the bottles contents from external contamination;
- The dropper device holder to which the dropper device is welded and which seals the bottle. The dropper device holder contains a porous material which controls the flow of eye drops onto the filter membrane and prevents the membrane from being in contact with the eye drops solution before first use.

Figure 1 ABAK® container



Each study site will receive one container (Final container).

Each of these containers contains two secondary containers:

- One container for treatment period Day 1 to Day 35 ;
- One container for treatment period Day 35 to Day 84.

Secondary containers for period Day 1 to Day 35 contain two bottles of the IMD. Secondary containers to be dispensed at Day 35 contain three bottles of the IMD.

Thus each patient receives up to five bottles of IMD during the study.

Bottles are labeled as shown below.

Figure 2 IMD: labeling of each primary bottle

For T2259:

Laboratoires THEA
12, rue Louis Blériot 63017 Clermont –Ferrand Cedex 2. FRANCE
Tel: +33 473 981 436

LT2259-001
Treatment Kit No.: KXXXX
Batch No.: XX Expiry Date: mm/YYYY

T2259
Eye drops/Ocular use
Dosage:
One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye.
Directions for use:
Do not allow the tip to come into contact with the eye or eyelids.
Put the cap back after use.

Keep at temperature below 25°C
Use within 2 months after opening.
For clinical trial use only.
Keep out of the reach of children.
For topical ocular use only.

Or

For Vismed® Multi:

Laboratoires THEA
12, rue Louis Blériot 63017 Clermont –Ferrand Cedex 2 - FRANCE
Tel: +33 473 981 436

LT2259-001
Treatment Kit No.: KXXXX
Batch No.: XX Expiry Date: mm/YYYY

Vismed®Multi
Eye drops/Ocular use
Dosage:
One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye.
Directions for use:
Do not allow the tip to come into contact with the eye or eyelids.
Put the cap back after use.

Keep at temperature below 25°C
Use within 2 months after opening.
For clinical trial use only.
Keep out of the reach of children.
For topical ocular use only.

Figure 3 Labeling of secondary containers for period Day 1 to Day 35 and Day 35 to Day 84

For T2259:

Laboratoires THEA- 12, rue Louis Blériot 63017 Clermont –Ferrand Cedex 2 - FRANCE Tel: +33 473 981 436 **LT2259-001** **Treatment Kit No.: KXXXX** Batch No.: XX Expiry date**:** mm/YYYY **Period Day 1 – Day 35** Cardboard box containing 2 vials of 10 ml of T2259 Eye drops/Ocular use Dosage: One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye. Directions for use: Do not allow the tip to come into contact with the eye or eyelids. Put the cap back after use. *Keep at temperature below 25°C* *Use within 2 months after opening.* *For clinical trial use only.* *Keep out of the reach of children.* *For topical ocular use only.* Prof/Dr _____ Tel:	Laboratoires THEA **LT2259-001** **Treatment: KXXXX** **PERIOD** **Day 1 – Day 35** **Batch No.: XX** **Expiry date:** **mm/YYYY**

Laboratoires THEA- 12, rue Louis Blériot 63017 Clermont –Ferrand Cedex 2 - FRANCE Tel: +33 473 981 436 **LT2259-001** **Treatment Kit No.: KXXXX** Batch No.: XX Expiry date**:** mm/YYYY **Period Day 35 – Day 84** Cardboard box containing 3 vials of 10 mL of T2259. Eye drops/Ocular use Dosage: One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye. Directions for use: Do not allow the tip to come into contact with the eye or eyelids. Put the cap back after use. *Keep at temperature below 25°C* *Use within 2 months after opening.* *For clinical trial use only.* *Keep out of the reach of children.* *For topical ocular use only.* Prof/Dr _____ Tel:	Laboratoires THEA **LT2259-001** **Treatment: KXXXX** **PERIOD** **Day 35 – Day 84** **Batch No.: XX** **Expiry date:** **mm/YYYY**

For Vismed® Multi:

Laboratoires THEA- 12, rue Louis Blériot 63017 Clermont – Ferrand Cedex 2 - FRANCE Tel: +33 473 981 436 **LT2259-001** **Treatment Kit No.: KXXXX** Batch No.: XX Expiry date**:** mm/YYYY **Period Day 1 – Day 35** Cardboard box containing 2 vials of 15 mL of Vismed® Multi Eye drops/Ocular use Dosage: One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye. Directions for use: Do not allow the tip to come into contact with the eye or eyelids. Put the cap back after use. *Keep at temperature below 25°C* *Use within 2 months after opening.* *For clinical trial use only.* *Keep out of the reach of children.* *For topical ocular use only.* Prof/Dr _____ Tel:	Laboratoires THEA **LT2259-001** **Treatment: KXXXX** **PERIOD** **Day 1 – Day 35** **Batch No.: XX** **Expiry date:** **mm/YYYY**

Laboratoires THEA- 12, rue Louis Blériot 63017 Clermont – Ferrand Cedex 2 - FRANCE Tel: +33 473 981 436 **LT2259-001** **Treatment Kit No.: KXXXX** Batch No.: XX Expiry date**:** mm/YYYY **Period Day 35 – Day 84** Cardboard box containing 3 vials of 15 mL of Vismed® Multi Eye drops/Ocular use Dosage: One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye. Directions for use: Do not allow the tip to come into contact with the eye or eyelids. Put the cap back after use. *Keep at temperature below 25°C* *Use within 2 months after opening.* *For clinical trial use only.* *Keep out of the reach of children.* *For topical ocular use only.* Prof/Dr _____ Tel:	Laboratoires THEA **LT2259-001** **Treatment: KXXXX** **PERIOD** **Day 35 – Day 84** **Batch No.: XX** **Expiry date:** **mm/YYYY**

Figure 4 Final packaging of IMD

Laboratoires THEA- 12, rue Louis Blériot
63017 Clermont –Ferrand Cedex 2 - FRANCE
Tel: +33 473 981 436

LT2259-001
Treatment Kit No.: KXXXX

Eye drops/Ocular use

This cardboard carton contains:
-2 cardboard boxes containing a total of 5 vials of T2259
-or 2 cardboard boxes containing a total of 5 vials of Vismed® Multi

Batch No.: **Expiry date:**

Dosage: One drop 2 to 4 times daily in the conjunctival cul-de-sac in each eye.

Directions for use:
Do not allow the tip to come into contact with the eye or eyelids.
Put the cap back after use.

Keep at temperature below 25°C
Use within 2 months after opening.
For clinical trial use only.
Keep out of the reach of children.
For topical ocular use only.

Prof/Dr _____ Tel:

2.7 Storage conditions and indications of use

T2259 should be used within 2 months after first opening of the ABAK® container. The IMD should be stored below 25°C and should not be used after the expiry date indicated on the outer cardboard box.

The expiry date (36 months) refers to the intact correctly stored packaging.

The IMD should not be used if the bottle is damaged.

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 Background

Dry eye disease (DED) is defined as a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (DEWS II 2017, Definition and Classification Report). The pathological process of DED is propagated by a chain of events that lead to ocular surface damage. Initially this gives rise to symptoms and compensatory responses, but it also generates inflammatory responses that ultimately lead to chronic ocular surface damage and self-perpetuate disease. The vicious circle of dry eye may be initiated by tear hyperosmolarity but also by different disorders such as ocular surface inflammation due to allergic eye disease, topical preservative toxicity, and xerophthalmia which is associated with a loss of conjunctival goblet cells or altered mucin expression (DEWS II 2017, Pathophysiology Report).

Two predominant and non-mutually exclusive categories of DED are aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE). ADDE describes conditions affecting lacrimal gland

function, while EDE is understood to occur with conditions affecting the eyelid (e.g. Meibomian gland dysfunction [MGD] and blink abnormalities) or the ocular surface (e.g. related to mucin deficiency or contact lens wear) (DEWS II 2017, Definition and Classification Report).

Large epidemiologic studies confirm that female sex and older age increase the risk for DED. Other substantiated risk factors include MGD, hematopoietic stem cell transplantation, computer use, Asian race, contact lens wear, Sjögren syndrome, environmental hazardous conditions such as pollution, low humidity, systemic connective diseases, certain classes of medications including antihistamines, antidepressants, anxiolytics and isotretinoin, and possibly androgen deficiency (DEWS II 2017, Epidemiology Report).

Regardless of how it is initiated and its aetiology, the clinical consequences of DED are the same at the ocular surface. These may include punctate epitheliopathy, filamentary keratitis, superior limbic keratitis, goblet cell loss, modification of the epithelial glycocalyx, lid parallel conjunctival folds, changes to Marx's line and MGD itself (DEWS II 2017, Pathophysiology Report).

Both discomfort and visual disturbance symptoms remain fundamental to DED. It causes irritation, pain and affects ocular and general health and well-being, the perception of visual function, and visual performance. Pain associated with DED can have psychological and physical impacts, while blurred vision may impose restrictions in daily life activities such as reading, driving, watching television, and operating smartphones (DEWS II 2017, Epidemiology Report). However, some DED patients exhibit signs of ocular surface disease, but report no symptoms of discomfort at the early stage of DED or at later stages due to reduced corneal sensitivity (DEWS II 2017, Definition and Classification Report).

Current management of DED is largely addressed by the suppression of contributing factors (e.g., medications) and prescription of a wide range of artificial tears (eyedrops, fluid solutions, or ophthalmic gels) (DEWS II 2017, Management and Therapy Report). One of the mainstays of the therapy is treatment with topical lubricants and artificial tears (Schmidl *et al.* 2015). The Management and Therapy Subcommittee of the International Dry Eye Workshop confirmed the place of choice of ocular lubricants, in the first step of DED management (DEWS II 2017, Management and Therapy Report).

3.2 Relevant pre-clinical data

An assessment of the biological safety of the T2259 eye drops was undertaken by Laboratoires Théa to address the biological risks based on the ISO 10993-1 requirements (T2259 BSA-Final). After a thorough review of published literature on the raw materials (trehalose and SH) and manufacturing processes of the T2259 device, a set of biocompatibility tests have been conducted on the T2259 device (Cytotoxicity, Sensitization, Skin irritation, Ocular irritation, Genotoxicity). T2259 device was macroscopically and microscopically well tolerated in albino rabbit eyes in an ocular irritation test, representative of clinical use that could be considered as a subacute toxicity study. The physical compatibility of T2259 device with rigid or soft contact lenses was also demonstrated so it can be considered that the use of T2259 device will not modify the physical and optical properties of contact lenses. Considering all aforementioned successful pre-clinical testing and justification, the safety profile of T2259 eye drops was established and can be considered biocompatible and suitable for use as intended in the human eye for the management of DED.

3.3 Relevant clinical data

The IMD T2259 is not CE-marked and no clinical data are available at this stage.
T2259 is a preservative-free combination of SH 0.2% and trehalose 6%, two efficient and safe lubricants with complementary modes of action.

Both main ingredients of T2259, SH and trehalose, are currently marketed by Laboratoires Théa as preservative-free ophthalmic solutions (Hyabak® for SH 0.15% and Thealoz® for trehalose 3%) with first indication in the management of DED. Hyabak® and Thealoz® are effective and safe to moisten and lubricate the eye in case of dryness or sensation of fatigue (Essa 2018; Schmidl *et al.* 2015; Brjesky *et al.* 2014; Ramoth *et al.* 2013; trial NCT01742884).

Notably, an ophthalmic solution combining SH 0.15% and trehalose 3% is also marketed by Laboratoires Théa (brand name Thealoz Duo® or Théalose®) for the protection, hydration and lubrication of the eye with moderate-to-severe dry eye syndrome (Thealoz Duo® instructions for use, 2015). The clinical experience with Thealoz Duo® has largely shown its performance and safety in the management of DED with the following main findings:

- Reduction of dry eye symptoms (stinging, itching, and blurred vision), better symptomatic relief with improvement of ocular surface disease index (OSDI), and a better patient satisfaction compared to Vismed® (SH 0.18%), particularly from the first month of treatment in moderate-to-severe DED (Chiambaretta *et al*. 2017; Doan *et al.* 2018);
- Greater improvement of patient satisfaction in patients with moderate-to-severe DED compared to Systane® (Pinto-Bonilla et al. 2015);
- Improvement in corneal and conjunctival staining, ocular signs (chemosis, conjunctival hyperaemia), Schirmer test, tear breakup time (TBUT) (Pinto-Bonilla *et al.* 2015);
- Higher increase in tear film thickness (TFT) and longer ocular residence time compared to Hydrabak® and Hyabak® in patients with moderate-to-severe DED (Schmidl *et al.* 2015);
- Absence of adverse event (AE) related to Thealoz Duo® reported in the studies mentioned above (Chiambaretta *et al.* 2017, Pinto-Bonilla *et al.* 2015, Schmidl *et al.* 2015). Based on Thealoz Duo® post-market surveillance data (PMS, Thealoz Duo v1.0 29092017), the ratio of the most frequently reported AEs (eye irritation, ocular hyperaemia, eye pain) is extremely low (<1/100,000 units sold). Theses AEs are non-serious.

Since investigational device T2259 (SH 0.2% and trehalose 6%) and Thealoz Duo® device (SH 0.15% and trehalose 3%; CE-marked since December 2012) share the same raw materials, the same dosage form as eye drop solutions and are both indicated for the management of DED, the clinical experience of Thealoz Duo® has been deemed relevant to support the expected performance and safety of the investigational device T2259.

Moreover, clinical investigations have been conducted on higher concentrations of trehalose or SH for dry eye patients, as described below.

Matsuo and colleagues showed that trehalose at 50 mM (1.7%), 100 mM (3.4%) or 200 mM (6.9%) prevents human corneal epithelial cells in culture from death by desiccation (Matsuo *et al.* 2002). In patient with moderate-to-severe DED, both trehalose 100 and 200 mM were

effective in improving the fluorescein and rose bengal staining scores of the ocular surface at weeks 2 and 4 compared with the control saline solution (Matsuo *et al.* 2002). Compared to baseline, TBUT significantly improved at weeks 2 and 4 with trehalose 100 and 200 mM, but not with saline. No adverse effects were noted in eyes receiving trehalose during the 4-week period. A 6-month follow-up of 20 patients treated with either trehalose 100 or 200 mM reported two patients with redness in the inferior palpebral conjunctiva after a few months of treatment with 200 mM trehalose (Matsuo *et al.* 2004).

An efficacy and safety comparison of 0.2% and 0.18% HA in moderate-to-severe DED patients reported the non-inferiority of 0.2% HA compared to 0.18% HA for the reduction of ocular surface lesions (Gross *et al.* 2017). A trend in favour of 0.2% HA was shown in terms of corneal and conjunctival staining scores at D35 and D84, and improvement of symptoms (particularly pain). No serious AE was reported. Among the 5 non-serious AEs reported during the study, 1AE (episodic allergy) was reported in the 0.2% HA group and 4 AEs (2 ocular irritations, 1 grittiness exacerbation, and 1 ocular fatigue) in the 0.18% HA group. A meta-analysis including 18 clinical trials compared the performance of SH (0.1 to 0.4%) *vs* alternative lubricant preparations in the treatment of DED (Ang *et al.* 2017). The majority of the studies showed superiority of SH over other treatments in improving ocular staining and symptoms. Particularly, studies which demonstrated superiority of SH for the improvement of tear osmolarity appeared to use higher concentrations (0.2 to 0.4%) compared to the other studies (0.1 to 0.18%).

Considering that higher concentrations of both trehalose (6%) and SH (0.2%) could have potential clinical benefits for the management of moderate-to-severe DED, Laboratoires Théa thus has decided to conduct a multicentre, randomised, investigator-masked, parallel-group study to evaluate the performance and safety of T2259 *vs* Vismed® Multi eye drops.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL MEDICAL DEVICE AND CLINICAL INVESTIGATION

4.1 Anticipated clinical benefits

Based on their mechanical and hydrating properties, hyaluronic acid solutions are widely used directly on the ocular surface at low concentrations or during ocular surgery as viscoelastics. Numerous ophthalmic solutions containing hyaluronic acid (e.g. Biolan®, Dropstar®, Dropyal®, Hyalistil®, Hylan Stulin®, Hylo-Comod®, Hyal-Drop®, Hyluprotect®, Ialurex®, Lacrycon®, Lalurex®, Vismed®, Vislube®, Xidan®) have been approved in Europe for dry eye treatment or for contact lens hydration and ocular surface hydration.

Trehalose 3% has also been approved as ocular lubricant effective and safe to moisten and lubricate the eye in case of dryness or sensation of fatigue. Laboratoires Théa is marketing both 0.15% SH (Hyabak®) and 3% trehalose (Thealoz®).

Notably, the combination of hyaluronic acid (0.15%) with trehalose (3%) (Thealoz Duo®) was shown to be a valuable agent in the management of DED symptoms and signs (Section 3.3).

Considering available data on the clinical performance of the similar device Thealoz Duo®, T2259 is expected to provide clinical benefits in the management of DED at least similar to that of Thealoz Duo®, including:

- Reduction of dry eye symptoms (stinging, itching, and blurred vision) and OSDI score, with great patient satisfaction;
- Improvement of ocular signs (chemosis, conjunctival hyperaemia), corneal and conjunctival staining, Schirmer test, TBUT, and increase in TFT;
- Long ocular residence time.

4.2 Anticipated adverse device effects

Based on pre-clinical data available for T2259 (Investigator's Brochure Section 4.1), the safety profile of the investigational device T2259 was established and T2259 can be considered biocompatible and suitable for use as intended (not cytotoxic, eye and skin non-irritant, not a sensitizer and non-mutagenic). Moreover, T2259 is compatible with contact lenses (Investigator's Brochure Section 4.2).

The excipients of the T2259 eye drops (trometamol, sodium chloride, hydrochloric acid and water for injections) are well-known and commonly used in ophthalmic formulations and the absence of preservative should contribute to an acceptable safety profile of the proposed medical device (Investigator's Brochure Section 3.3).

Literature and PMS data for the similar device Thealoz Duo® reported mostly no SAEs (Investigator's Brochure Sections 6.2.2 and 6.2.3). According to PMS data, adverse effects reported for Thealoz Duo® are very rare (frequency <1/100000). T2259 may cause mild eye irritation and/or ocular hyperaemia, although this might be very unusual. Of note, 2 cases of redness in the inferior palpebral conjunctiva were reported in the literature for 200 mM (6.9%) trehalose.

Considering the absence of SAEs in published clinical studies and during PMS for the similar device Thealoz Duo®, no serious adverse effects are expected with T2259.

4.3 Residual risks associated with the IMD

All identified risks meet the acceptability criteria defined by the European Norms NF EN ISO 14971 (January 2013, Medical Devices-Application of Risk Management to Medical Devices).

All residual risks highlighted in the Medical Device Risk Management Analysis dated on October 2017 are of class III (acceptable) except for the risks of misuse and non-sterile product which remain of class II (acceptable risk in specified conditions).

Control measures for these latter risks were documented in the Risk Management Analysis Report. All the possible warnings have been put in place in the leaflet (Appendix I) provided to each patient to avoid misuse (see Section 4.6). This hazard was considered as not probable in the normal condition of use. For the risk of non-sterile product, warning messages on the leaflet specified that the product should not be used if the safety ring is damaged, or if the bottle is damaged. Post-market data on similar products showed no contamination of the bottle detected up-to-now due to its design (0.2 µm filter). The ratio benefit/risk is positive for the patient.

4.4 Risks associated with participation in the clinical investigation

The residual risks of level II and III associated with participation in the clinical investigation include the following:

- Potential interactions with concomitant medications (see Section 4.5);
- Potential inadequate storage conditions (see Section 4.6);
- Potential allergic reaction (see Section 4.6);
- Potential misuse of the device (see Section 4.6);
- Potential use of damaged or contaminated device (see Section 4.6).

4.5 Possible interactions with concomitant medical treatments

To avoid possible interactions with a concomitant treatment, patients should be asked to wait at least 10 minutes between using two different eye products (see Section 4.6).

T2259 device is compatible with contact lenses.

4.6 Control and minimisation of risks

According to the steps defined in the RMP established for T2259, all identified risks meet the acceptability criteria defined by ISO 14971 (see Section 4.3).

In addition to the compliance with relevant norms, availability of relevant supporting data and adequate manufacturing, the following warnings and precautions for use are mentioned in the leaflet to optimise patients' use of the IMD (see Appendix I):

- Regarding the risk of interaction with concomitant medications, the "Interactions" section specifies that the patient is required to wait at least 10 minutes between applications of T2259 and any other eye drops. The Sponsor has conducted non-clinical studies and approved the physical compatibility of T2259 with contact lenses;

- Regarding the risk of inadequate storage, the "Storage of the product" section specifies that the patient should store the product below 25°C;
- Regarding the risk of potential allergic reactions, the "Special warning and special precautions for use" section specifies that the patient should not use the IMD in case of allergy to one of the components of T2259;
- Regarding a potential misuse of the device, the "Special warnings and special precautions for use" section specifies that the patient should not inject or swallow the product, and keep out of the sight and reach of children. The dosage is specified as "1 drop in each eye, 2 to 4 times daily". The storage condition of the product is specified with a warning "do to use the product after the expiry date clearly marked on the outer carton";
- Regarding a potential use of damaged or contaminated device, the "Special warnings and special precautions for use" and "Method and route of administration" sections specify that the patient should put the cap back after use, not use the bottle if it is damaged, avoid touching the eye or eyelids with the tip of the bottle and wash hands well before use.

4.7 Risk-to-benefit rationale

Results of this risk analysis confirm that T2259 has an acceptable benefit/risk profile. The expected clinical benefits of T2259 considered together with the potential residual risks represent a positive risk/benefit ratio.

5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 Objectives, primary and secondary

The primary objective of the investigation is to demonstrate the performance of T2259 versus Vismed® Multi as non inferiority.

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

5.2 Hypotheses, primary and secondary, to be accepted or rejected by statistical data from the clinical investigation

The primary hypothesis is the non-inferiority of T2259 compared to Vismed® Multi. 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 on Day 35. If the upper bound is no higher than two 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.

5.3 Claims and intended performance of the IMD that are to be verified

T2259 eye-drops are intended to protect, hydrate and lubricate the eye.

5.4 Risks and anticipated adverse device effects that are to be assessed

There are no specific risks and anticipated adverse device effects to be assessed during this investigation.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 General

The chosen methodology and criteria correspond to the standard usually used in the recent clinical trials in DES (HAS Optive, 2011).

Thus, this is a multicentre, randomized, investigator-masked, two parallel groups (T2259 versus Vismed® Multi) investigation in dry eye patients with superficial keratitis. The investigation will be performed in France, in Spain, in Slovakia and in Poland.

Multicenter (and multi-investigator) design will provide the possibility of recruiting the subjects from a wider population and of using the device in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. In this case, the involvement of a number of investigators also gives the potential for a wider range of clinical judgment concerning the value of the therapeutic intervention. In addition, it is also a practical mean of accruing sufficient subjects to satisfy the study objective within a reasonable timeframe.

Because of a different visual aspect of the tested eye-drops, a double-masked comparison is not possible. Thus an investigator-masked method will be used. The identity of the IMD provided to each patient and the data concerning the instillation schedule will not be known by the investigator in charge of the examinations and of performance and safety assessments. The two different treatment units will be identical in external appearance in order to respect the randomisation. A second investigator (a physician) will dispense medications allowing to mask the first ophthalmologist investigator (who will be in charge of all examinations and assessments), and patients will be instructed not to disclose drug information with other staff members or the first investigator.

Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the treating device from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. The chosen comparator, Vismed® Multi (Appendix II), of which performance has been demonstrated in the treatment of moderate to severe DES, is considered a reference product (HAS Optive, 2011). Previous clinical data have demonstrated that Thealoz Duo® is at least as efficacious as Vismed® and is better appreciated by both the investigator and the patient, better tolerated, with advantageous effects on DED symptoms (Chiambaretta *et al*. 2017).

With DES being a known short term fluctuating pathology (Baudouin 2001), it has been decided to define the primary end-point for performance after 35 days. This treatment period is considered sufficient to allow for the evaluation of the performance of this kind of treatment. Nevertheless, performance and safety will also be assessed after the classical instillations period of 3 months of treatment (DEWS I, 2007).

Patients will be randomised after a run-in period of 7 to 10 days, during which they will use only preservative-free artificial tears (Hydrabak®) as ocular treatment. Then, they will be treated with either T2259 or the reference product (Vismed® Multi) for 84 days (± 7 days).

Performance criteria will be assessed on Day 8 ± 1 day (visit 3/ optional visit), Day 35 ± 3 days (visit 4) and Day 84 ± 7 days (visit 5). Local tolerance will be assessed by the investigator on Day 35 ± 3 days (visit 4) and Day 84 ± 7 days (visit 5). Ocular symptoms (except upon instillation, not assessed at inclusion) as well as adverse events (AEs) will be assessed at all investigation visits.

The investigation flow chart is described in Table 2, page 12.

6.2 Description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking

6.2.1 Randomisation

A patient who has given his/her written informed consent and who is included in the study will be assigned a specific treatment number.

Random allocation of patients in the T2259 group or Vismed® Multi group will 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 is generated by the CRO in charge of the statistics. Patients will be randomised on a 1:1 basis to T2259 or comparator product respectively. The IP will be allocated to the patients according to randomisation using an interactive response system (IWRS).

Randomisation will occur at the randomisation visit (Day 1; Visit 2) after all screening procedures have been performed and eligibility for the study confirmed. The patient who meets the eligibility criteria will be 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 will allocate 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.

If a discontinued patient needs to be replaced, the next available treatment number in the centre will be used.

6.2.2 Masking

This will be an investigator-masked clinical study. The **first ophthalmologist investigator** will remain masked to the IMD. He will NOT dispense or receive the returned IMD from the patients.

Masking will be achieved by providing the 2 IMD (T2259 and Vismed® multi) in identical cardboard and by identifying each IMD by a treatment number.

The **second ophthalmologist** investigator will be in charge of IMD dispensation, accountability and of patient questioning.

The code should not be broken except:

- In case of a medical emergency (where knowledge of the IMD received would affect the treatment of the emergency);
- Or when it is a regulatory requirement.

If an emergency code breaking becomes necessary, the investigator should notify the Sponsor, if possible, prior to breaking the code. The investigator and/or pharmacist are responsible for accessing the Interactive Web Response System to obtain the identity of the IMD allocated to the patient. When a code is broken, the date, time and reason must be recorded in the patient's source documentation as well as in the e-CRF, and in any associated AE report. The identity of the IMD should not be disclosed in these documents.

Further to a USADE assessment by the Global Drug Safety & Medical Information Department, the code might be broken for reporting purposes. The relevant Laboratoires Théa, CRO, and investigator staff remains unaware of the identification of the IMD.

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

6.2.3 Dispensing

The IMD must be dispensed in accordance with the protocol. For each patient included, a treatment kit will be provided and contain enough medication for the whole treatment period.

During the randomisation visit (Day 1), the investigator responsible for IMD dispensation (other than the first ophthalmologist investigator) will open the treatment unit corresponding to the allocated treatment number. Patient numbers must be allocated in an ascending order using the next available consecutive number (to be recorded in the e-CRF). Then, the site team member will provide the patient with the treatment kit to be taken home.

During the whole investigation treatment period, the evaluating ophthalmologist investigator will remain masked to the IMD.

Two dispensations will be performed as follow:

- On Day 1: one box containing enough medication for the treatment period Day 1 to Day 35 will be provided to the patient;
- On Day 35: one box containing enough medication for the treatment period Day 35 to Day 84 will be provided to the patient.

The site team member will instruct patients on the method of instilling the doses.

Patients will be instructed to return unused IMD as well as empty/partially empty containers of used IMD.

A daily record of the IMD containers dispensed to the patient will be maintained by the site team in the Drug Accountability Form.

6.3 Primary and secondary endpoints, with rationale for their selection and measurement

6.3.1 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 D35 in the worst eye.

6.3.2 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) / optional examination 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 Day 84;
- 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.

6.3.3 Safety endpoints

Other evaluation parameters are:

- Ocular symptoms 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 (ADE/SADE).

These endpoints have been chosen considering the clinical literature review of Thealoz Duo® (Pinto-Bonilla et al. 2015; Schmidl et al. 2015; Schmidl et al. 2016-abstract; Chiambaretta et al. 2017). They are clinically relevant, clearly defined and assessed at a specified time point in order to provide clinical evidence on the performance and tolerance of the T2259 device in the target population for the management of the ocular signs and symptoms of patients with dry eye disease.

6.4 Methods and timing for assessing, recording, and analysing variables

Five visits are scheduled during the course of the investigation as presented below:

- Visit #1: selection visit (between day 1 -10 and day 1 -7);
- Visit #2: randomisation visit (day 1);
- *Visit #3: day 8 ± 1; Optional visit (if the investigator and/or the patient thinks it is necessary)*
- Visit #4: day 35 ± 3 days;
- Visit #5: final visit (day 84 ± 7 days).

Visits V2, V3, V4 and V5 should be performed at the same hour (±4 hours).Investigations are to be conducted as per the schedule of investigation procedures detailed in Table 2, page 12.

6.4.1 Selection visit (visit #1): Day 1 -10 days/Day1 -7 days

Preliminary remark: Informed consent

The patient (or/and the legally acceptable representative) must be verbally informed about the investigation and must be given a copy of the patient information sheet. The patient (or/and the legally acceptable representative) must be given the opportunity to ask questions, and have reasonable time for reflection before giving his/her informed consent.

Written informed consent must be obtained prior to initiation of any investigational procedures or any discontinuation of current medication. No measures whatsoever described in the CIP shall be undertaken without such consent indicating that the patient (or/and the legally acceptable representative) has been given both verbal and written information about the investigation and the IMD.

The informed consent form shall be signed and dated by the patient (or/and the legally acceptable representative) and the investigator or a physician designated by the investigator. Two original consent forms will be signed and one shall be included in the investigator's

investigation file, the other one shall be given to the patient (or/and the legally acceptable representative).

Visit #1 will consist of the following procedures and examinations to be done according to the following order and in each eye for ocular assessments.

By **the investigator** in charge of all examinations and safety assessment during the investigation:

- Information of the patient and signature of the informed consent;
- Demography;
- Questioning about ocular medical and surgical history;
- Questioning about systemic medical and surgical history;
- Questioning about previous and concomitant ocular and non-ocular treatments;
- History of Dry Eye;
- Completion of DEQ-5 questionnaire;
- Questioning about ocular symptoms;
- Measurement of the far best-corrected visual acuity;
- Measurement of conjunctival hyperaemia with McMonnies photographic scale;
- Urinary pregnancy test (only for childbearing potential women)
- Slit lamp examination for measuring:
  - TBUT,
  - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal staining by lissamine),
  - Van Bijsterveld score (lissamine green staining) / optional examination;
- Verification of inclusion/exclusion criteria;
- Dispensation of Hydrabak® for the run-in period.

6.4.2 Randomisation visit (visit #2): Day 1

Visit #2 will take place 7 to 10 days after the selection visit (visit #1) and will consist of the following procedures and examinations (to be done according to the following order and in **each eye** for ocular assessments).

By **the first investigator** in charge of all examinations and safety assessment during the investigation:

- Questioning about Hydrabak® compliance during the run-in period;
- Questioning about concomitant ocular and non-ocular treatments;
- Questioning about AEs during the run-in period;
- Measurement of OSDI score;
- Questioning about ocular symptoms;
- Measurement of conjunctival hyperaemia with McMonnies photographic scale;
- Slit lamp examination for measuring:
  - TBUT,
  - Oxford 0-15 grading scheme (corneal staining by fluorescein, temporal and nasal staining by lissamine),
  - Van Bijsterveld score (lissamine green staining) / optional examination;
- Schirmer test (without anaesthesia);
- Adverse events;
- Verification of inclusion/exclusion criteria;
- Randomisation.

At investigation sites equipped with Optical Quality Analysing System (OQAS):

- Evaluation of OSI using double pass aberrometry.

For patients with severe Dry Eye, defined as OSDI≥33 and/or Corneal Fluorescein Staining ≥ 3

- Impression cytology (for HLA-DR).

By **the second investigator** responsible for dispensation:

- Explanations of dosing regimen for IMD;
- IMD dispensation for the period Day 1 to Day 35 according to allocated treatment number.

6.4.3 Visit #3: Day 8 ± 1 day (optional visit)

Visit #3 will take place 6 to 8 days after the randomisation visit (visit #2) and can be performed if investigator and/or patient thinks it is necessary.

This visit will consist of the following procedures and examinations (to be done according to the following order and in **each eye** for ocular assessments).

By **the first investigator** in charge of all examinations and safety assessment during the investigation:

- Questioning about concomitant ocular and non-ocular treatment;
- Questioning about AEs between Day 1 and Day 8;
- Measurement of OSDI score;
- Questioning about ocular symptoms;
- Measurement of conjunctival hyperaemia with McMonnies photographic scale;
- Slit lamp examination:
  - TBUT,
  - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal staining by lissamine),
  - Van Bijsterveld score (lissamine green staining) / optional examination;
- Schirmer test (without anaesthesia).

By **the second investigator** responsible for dispensation:

- Questioning about AEs between Day 1 and Day 8,
- Questioning about ocular symptoms upon instillation.

6.4.4 Visit #4: Day 35 ± 3 days

Visit #4 will take place 35 days ± 3 days after the Randomisation visit (visit #2) and will consist of the following procedures and examinations (to be done according to the following order and in **each eye** for ocular assessments).

By **the first investigator** in charge of all examinations and safety assessment during the investigation:

- Questioning about concomitant ocular and non-ocular treatment;
- Questioning about AEs between Day 1 or Day 8 (optional visit) and Day 35;
- Completion of DEQ-5 questionnaire;
- Measurement of OSDI score;
- Questioning about ocular symptoms;
- Measurement of the far best-corrected visual acuity;
- Measurement of conjunctival hyperaemia with McMonnies photographic scale;
- Urinary pregnancy test (only for childbearing potential women)
- Slit lamp examination with fluorescein and lissamine green stainings for measuring:
  - TBUT,
  - Oxford 0-15 grading scheme (corneal staining by fluorescein, temporal and nasal staining by lissamine),
  - Van Bijsterveld score (lissamine green staining) / optional examination;
- Schirmer test (without anaesthesia);
- Tolerance assessments by the patient and investigator;
- Performance assessment by the investigator;

At investigation sites equipped with Optical Quality Analysing System (OQAS):

- Evaluation of OSI using double pass aberrometry.

By the **second investigator** responsible for dispensation:

- Questioning about AEs between Day 1 or Day 8 (optional visit) and Day 35;
- Questioning about dose regimen compliance;
- Questioning about ocular symptoms upon instillation;
- IMD dispensation for the period Day 35 to Day 84 according to allocated treatment unit number.

6.4.5 End of investigation visit (visit #5): Day 84 ± 7 days

Visit #5 will take place 84 days ± 7 days after randomisation visit (visit #2) and will consist of the following procedures and examinations (to be done according to the following order and in both eyes for ocular assessments).

By **the first investigator** in charge of all examinations and safety assessment during the investigation:

- Questioning about concomitant ocular and non-ocular treatment;
- Questioning about AEs between Day 35 and Day 84;
- Questioning about ocular symptoms;
- Completion of DEQ-5 questionnaire;
- Measurement of OSDI score;
- Measurement of the far best-corrected visual acuity (Snellen chart);
- Measurement of conjunctival hyperaemia with McMonnies photographic scale;
- Urinary pregnancy test (only for childbearing potential women)
- Slit lamp examination for measuring:
  - TBUT,
  - Oxford 0-15 grading scheme (corneal staining by fluorescein, temporal and nasal staining by lissamine green),
  - Van Bijsterveld score (lissamine green staining) / optional examination;
- Schirmer test (without anaesthesia);
- Tolerance assessment by patient and investigator;
- Performance assessment by investigator;
- Adverse events.

At investigation sites equipped with Optical Quality Analysing System (OQAS):

- Evaluation of OSI using double pass aberrometry.

For patients with severe Dry Eye, defined as OSDI≥33 and/or Corneal Fluorescein Staining ≥ 3 at baseline visit (Day 1):

- Impression cytology (for HLA-DR).

By the **second investigator** responsible for dispensation:

- Questioning about AEs between Day 35 and Day 84;
- Questioning about dose regimen compliance;
- Questioning about ocular symptoms upon instillation.

6.5 Procedures for the replacement of patients

The number of randomised patients will be followed in order to obtain 76 evaluable patients in the PP population.

6.6 IMD

6.6.1 Description of the exposure to the IMD

IMD will be administered by the patient every day for 84 ± 7 days, one drop in each eye 2 to 4 times daily into the lower conjunctival sac of each eye.

There will be two treatment groups:

- T2259;
- Reference product: Vismed® Multi (Appendix II)

A detailed description of T2259 is available in Section 2, page 21. Vismed® Multi is described below.

6.6.2 Justification of the choice of comparator(s)

Vismed® Multi (Horus Pharma, France) is a sterile, preservative-free, hypotonic (about 200 mOsmol/L) solution of 0.18% SH, packaged in a multidose container. Vismed® Multi is currently marketed in Europe under the CE mark as a viscoelastic lubricant eye drop (CE marking: IIb Class, notification by TÜV PRODUCT SERVIC GMB (0123), Germany). Vismed® Multi has obtained its inscription on the List of Products Reimbursed by French Social Security (LPPR) in July 2007 with the indication “Symptomatic treatment of eye dryness with keratitis or keratoconjunctivitis sicca, in third intent after failure of low viscosity tears substitutes and gels”.

Table 4 details the composition and function of the comparative device Vismed® Multi. Vismed® Multi is purchased from Horus Pharma.

Packaging and labelling is provided in Section 2.6 page 23.

Table 4 Vismed® Multi

Name of ingredients	Formula Per 100 mL
HA, sodium salt	0.18%
Sodium chloride	0.279%
Potassium chloride	0.103 g
Magnesium chloride	0.0092%
Calcium chloride	0.0089%
Disodique hydrogenophosphate,	0.032%
Sodium citrate	0.0026%
Hydrochloric acid	Ad pH 7.2 – 7.4
Purified water, to	100 mL

6.6.3 List of any other medical device or medication to be used during the clinical investigation

During the run-in period, patients will be asked to use only Hydrabak® eye dops (Laboratoires Théa, France).

Hydrabak® are unpreserved NaCl 0.9 % eye drops in an ABAK® system vial containing 10 mL of solution. Hydrabak® will be provided by Laboratoires Théa.

During the selection visit (Day1 -10/Day 1 -7), the investigator in charge of all examinations and assessments will provide all patients with one bottle of Hydrabak® for the run-in treatment period between Day 1-10/Day 1-7 and Day 1.

Table 5 Run-in Medical device Sodium Chloride (Hydrabak®)

Name of the ingredients	Formula per 100 mL	Function
Sodium chloride	0.9% g	Active ingredient
Sodium dihydrogen phosphate	0.067%	Buffer
Disodium phosphate rate	0.317%	Buffer
Water for injections	Ad 100 mL	Vehicle

6.6.4 Number of IMD to be used, together with a justification

During the investigation, each patient will receive the IMD (five bottles of T2259 or of Vismed® Multi) and one bottle of Hydrabak® to cover run-in and active treatment period.

6.7 Patients

6.7.1 Inclusion criteria for patient selection

6.7.1.1 Selection visit

The following inclusion criteria have to be met at selection visit:

- 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 investigation selection.

6.7.1.2 Randomisation visit

The following inclusion criteria have to be met at randomisation visit:

- 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;
- Diagnosis of moderate to severe Dry Eye Syndrome defined by OSDI Score ≥ 23;
- Patient 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 (e.g. patients with superficial keratitis),

  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.

6.7.2 Exclusion criteria for subject/patient selection

Meeting one of the following exclusion criteria will not allow for inclusion of the patient.

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 investigation or likely to interfere with the investigation results or the patient safety according to investigator judgment;
- Allergic rhinitis active or susceptible to reactivate during the investigation;
- Any other medical or surgical history, disorder or disease susceptible to require or to modify systemic medication during the investigation (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 investigation 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 investigation;
- Patient previously randomised in this investigation;
- Patient being institutionalised because of legal or regulatory order, inmate of psychiatric wards, prison or state institutions, or employee of the investigation sites or of the sponsor's company;
- Patient not covered by the French government health care;
- Patient under guardianship/ward of court;

- Patient with previous, current prohibited listed treatment (or prohibited modification of treatment regimen, see Table 1, page 11).

6.7.3 Criteria and procedures for patient withdrawal or discontinuation

Patient should be withdrawn from the investigation if, in the opinion of the investigator, there is any situation or condition which puts the subject at significant risk. Any patient may voluntarily discontinue the investigation at any time he or she chooses (Declaration of Helsinki), without prejudice. The investigator may choose to discontinue a patient for reasons related to the investigation product (AE or unsatisfactory therapeutic response). In either event, details should be recorded in the e-CRF and reported separately.

Possible reasons for withdrawal include the following:

- AEs leading to discontinuation from the investigation;
- Treatment failure: the patient or the physician does not feel that the IMD has adequately relieved his/her symptoms;

  In case of aggravation of dry eye syndrome or superficial keratitis, an adverse event form must be completed by the investigator and all the investigations planned at the final visit must be done (premature withdrawal visit). The investigator will prescribe the best appropriate treatment to the patient.

- Patient's request;
- Other reason.

If the patient is lost to follow-up, the investigator must contact his/her patient to obtain more information (by phone, fax, regular mail or email…).

If a patient discontinues prematurely the investigation, the investigator will perform all the investigations planned at the final visit and will prescribe the best appropriate treatment to the patient.

6.7.4 Point of enrolment

Patients are to be enrolled at about 35 investigational sites in France, Spain, Slovakia and Poland.

6.7.5 Total expected duration of the clinical investigation

This investigation is planned to start in October 2018 and to be completed in December 2020.

6.7.6 Expected duration of each subject/patient's participation

The treatment period for each patient is 84 ± 7 days for a total investigation duration of 101 days.

6.7.7 Number of patients required to be included in the clinical investigation

A total of 90 patients has to be randomised in order to have 76 evaluable patients (38 per group) for the PP analysis.

6.7.8 Estimated time needed to select this number (i.e. enrolment period)

The enrolment period is estimated at 20 months.

6.8 Procedures

Description of all the clinical-investigation-related procedures that subjects/patients undergo during the clinical investigation

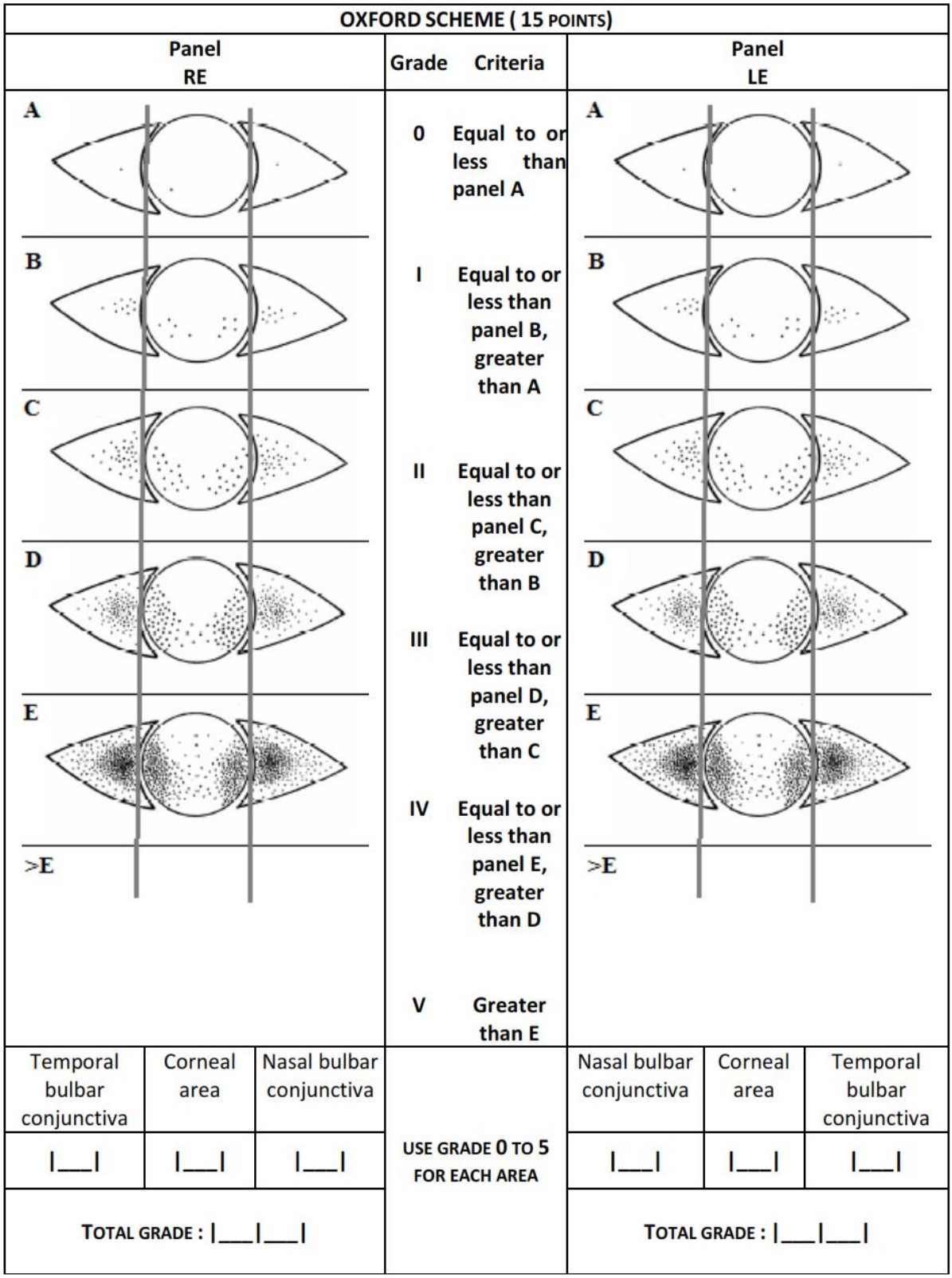
6.8.1 Performance measures

6.8.1.1 Primary performance variable

The primary performance variable will be the total ocular staining grade using Oxford 0-15 grading scheme (assessing the staining in corneal area from fluorescein staining and in temporal and nasal areas from lissamine green staining) (Figure 5).

The Oxford score will be measured at each visit in each eye. The value at Day 1 will be the baseline value.

Figure 5 Oxford 0-15 grading scheme



6.8.1.2 Other performance variables

6.8.1.2.1 OSDI

The impact of the disease on the patient's daily activities will be assessed by the Ocular Surface Disease Index (OSDI) described in Figure 6. The value at Day 1 will be the baseline value.

Figure 6: Ocular Surface Disease Index (OSDI)

Give the patient an OSDI questionnaire and ask him to complete it (self-questionnaire)**, and calculate the OSDI score.**

	Have you experienced any of the following during the last week? *La semaine passée, avez-vous eu les problèmes suivants?*	All of the time *Tout le temps*	Most of the time *La plupart du temps*	Half of the time *La moitié du temps*	Some of the time *De temps en temps*	None of the time *Jamais*
1	Eyes that are sensitive to light? *Sensibilité des yeux à la lumière ?*	4	3	2	1	0
2	Eyes that feel gritty? *Sensation de sable dans les yeux ?*	4	3	2	1	0
3	Painful or sore eyes? *Douleur ou irritation au niveau des yeux ?*	4	3	2	1	0
4	Blurred vision? *Vision trouble ?*	4	3	2	1	0
5	Poor vision? *Mauvaise vision ?*	4	3	2	1	0

Subtotal score for answers 1 to 5 |__|__| (A)

	Have problems with your eyes limited you in performing any of the following during the last week? *La semaine passée, les problèmes que vous avez aux yeux vous ont-ils gêné (e) pour…*	All of the time *Tout le temps*	Most of the time *La plupart du temps*	Half of the time *La moitié du temps*	Some of the time *De temps en temps*	None of the time *Jamais*	N/A *Non concerné(e)*
6	Reading? *Lire?*	4	3	2	1	0	N/A
7	Driving at night? *Conduire de nuit?*	4	3	2	1	0	N/A
8	Working with a computer or bank machine (ATM)? *Utiliser un ordinateur ou un distributeur automatique de billets ?*	4	3	2	1	0	N/A
9	Watching TV? *Regarder la television?*	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 |__|__| (B)

	Have your eyes felt uncomfortable in any of the following situations during the last week? *La semaine passée, avez-vous eu une sensation désagréable au niveau des yeux…*	All of the time *Tout le temps*	Most of the time *La plupart du temps*	Half of the time *La moitié du temps*	Some of the time *De temps en temps*	None of the time *Jamais*	N/A *Non concerné(e)*
10	Windy conditions? *Quand il y avait du vent?*	4	3	2	1	0	N/A
11	Places or areas with low humidity (very dry)? *Quand vous étiez dans un endroit peu humide (air très sec)?*	4	3	2	1	0	N/A
12	Areas that are air conditioned? *Quand vous étiez dans un endroit climatisé?*	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 |__|__| (C)

Add subtotals A, B and C to obtain D
(D = sum of scores for all questions answered) |__|__|__| (D)

Total number of questions answered
(Do not include questions answered N/A) |__|__| (E)

$$\text{OSDI} = \frac{\text{Sum of scores (D)} \times 25}{\text{Number of questions answered (E)}} = \frac{|\_\_|\_\_|\_\_|}{|\_\_|\_\_|} = |\_\_|\_\_|\_\_|.$$

6.8.1.2.2 DEQ-5 Questionnaire

The value at Selection visit will be the baseline value.

Figure 7: DEQ-5 Questionnaire for Dry Eye Disease/Ocular Surface Disease

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, **how often** did your eyes feel discomfort?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly
   b. When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

Never have it	Not at all Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly
   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at all Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Question about **WATERY EYES**:
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
___+___+___+___+___= ____

6.8.1.2.3 Van Bijsterveld score / optional examination

Total ocular staining will also be assessed by the Van Bijsterveld score from the lissamine green staining.

It will be measured at each visit. The value at Day 1 will be the baseline value.

Impregnated paper strips Lissaver Plus will be used for staining, put in the same area as paper strip for Schirmer test. Reading will be performed between 1 and 4 minutes after stain to optimize staining (a chronometer will be used). The eye will be then examined at the slit lamp. Ocular surface will be observed starting with a low illumination possibly under red light (intense or bright illumination will diminish contrast and underestimate the degree of staining). The level of light may be increased until the staining is the most visible.

The evaluation of the test will be performed according to the Van Bijsterveld score (Figure 8). The corneo-conjunctival exposed surface is separated in three parts: nasal bulbar

conjunctive, corneal area, and temporal bulbar conjunctive. The following score will be attributed to each of these parts with the help of a visual figure representing each degree of staining:

(0) = No staining;

(1) = Some punctuations;

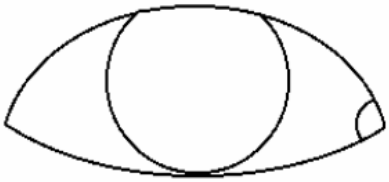
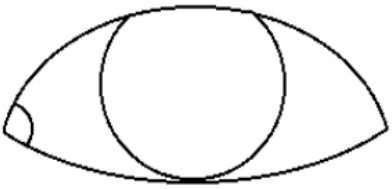
(2) = Well defined punctuations;

(3) = Total staining.

The total score is the addition of the scores obtained in the three parts (nasal, corneal and temporal).

Figure 8: Van Bijsterveld score

Assessment should be made between 1 and 4 minutes after Lissamine staining.

RE			LE		
Temporal bulbar conjunctiva	Corneal area	Nasal bulbar conjunctiva	Nasal bulbar conjunctiva	Corneal area	Temporal bulbar conjunctiva
A	B	C	C	B	A
					
A	B	C	C	B	A
0 1 2 3 ☐	0 1 2 3 ☐	0 1 2 3 ☐	0 1 2 3 ☐	0 1 2 3 ☐	0 1 2 3 ☐
Global Score = A+B+C =			**Global Score = C+B+A =**		

Score the **punctuation** using the scale of 0 to 3:

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

6.8.1.2.4 Schirmer test without anaesthesia

The Schirmer test will be conducted in a dimly lit room. Whilst the patient looks upwards, the lower lid will be drawn gently downwards and temporally. The rounded bent end of a sterile strip will be hooked in the lower conjunctival sac over the temporal one-third of the lower eyelid margin. After 5 minutes have elapsed, the tear front will be measured.

This test will be performed in each eye at each visit. The value at Day 1 will be the baseline value.

6.8.1.2.5 Tear Break-Up Time (TBUT)

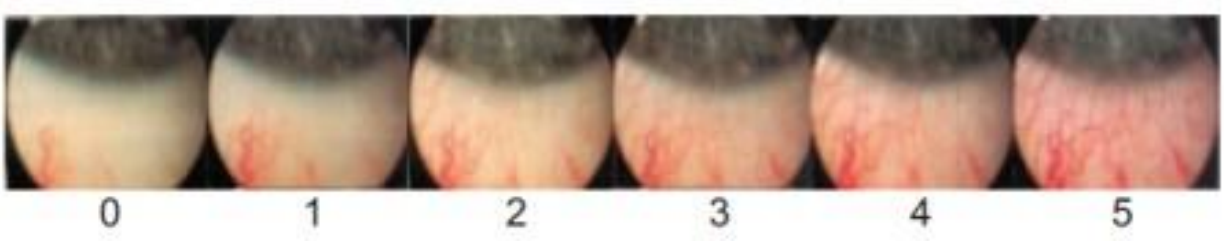
The TBUT will be done at each visit in each eye. The value at Day 1 will be the baseline value.

The tear break-up time will be measured three times during the first minute after the instillation of one drop of fluorescein. The TBUT value analysed will be the sum of the three measurements.

6.8.1.2.6 Conjunctival hyperaemia using Mac Monnies photographic scale

The conjunctival hyperaemia will be assessed using the Mac Monnies photographic scale in each eye (Figure 9). The value at Day 1 will be the baseline value.

Figure 9 Mac Monnies photographic scale



6.8.1.2.7 Ocular symptoms

Patient will be asked:
"How do you judge the severity of your following ocular symptoms ***WITHIN THE LAST 48 HOURS***?"
« Comment jugez-vous la sévérité de vos symptômes oculaires suivants ressentis ***DANS LES DERNIERES 48 HEURES****? »*

The severity of the following ocular symptoms (global evaluation for both eyes) will be assessed at each visit: **burning/irritation**, **stinging/eye pain**, **itching**, **eye dryness feeling, foreign body sensation**, **light sensitivity** and **fluctuating blurred vision** as follows:

(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.

6.8.1.2.8 Ocular symptoms upon instillation:

Patient will be asked: "Have you felt any unusual sensation upon instillation since the last visit?"

« Avez-vous ressenti une gêne/sensation oculaire inhabituelle à l'instillation depuis la dernière visite ?»
If the answer is yes, a table regrouping the functional ocular signs will have to be completed. Ocular symptoms upon instillation at Day 8 (optional), 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 limiting with daily activities.

6.8.1.2.9 Performance assessment by the investigator

The evaluation of the IMD performance will be assessed by the investigator, using the following rating scale:

- Very satisfactory;
- Satisfactory;
- Not very satisfactory;
- Unsatisfactory.

6.8.2 Safety measures

6.8.2.1 Far Best-corrected visual acuity in both eye

Far BCVA will be measured on each eye using the same chart throughout the study.

6.8.2.2 Tolerance assessment by the patient and the investigator

The IMD tolerance will be assessed on Day 35 and Day 84 using the following rating scale:

- Very satisfactory;
- Satisfactory;
- Not very satisfactory;
- Unsatisfactory.

6.8.2.2.1 Adverse events

Ocular and systemic AEs will be reported at each post selection investigation visit.

The handling of AEs is detailed in section **Erreur ! Signet non défini.**, page 71.

6.8.3 Prior and Concomitant Therapy

Concomitant medication is any treatment or medication given concurrently with the IMD or run-in treatment. Any other local or systemic medication necessary for the patient's welfare has to be recorded in the e-CRF.

In case of acute illness, any medication necessary for the patient's welfare has to be recorded in the e-CRF.

Medications forbidden during the investigation are presented in Table 1, page 11.

6.8.4 IMD compliance

Compliance with the IMD will be checked at Day 35 and Day 84 by the second investigator and reported in the e-CRF. In order to verify compliance, patients will be questioned during the protocol visits about their compliance with the IMD regimen. In addition, the patient will also have to report information about his compliance on a diary during the treatment period.

6.8.5 Other measures

6.8.5.1 Evaluation of Optical Scaterring Index (OSI) using double pass aberrometry

At investigational sites equipped with the Optical Quality Analysis System (OQAS, Visiometrics, Costa Mesa, CA, USA), evaluation of OSI will be performed at Day 1, Day 35 and Day 84 using the double pass aberrometry to assess the presence of cataract.

The double-pass technique has been shown to be a useful tool for comprehensively evaluating the optical quality of the eye (Logean E *et al.* 2008 ; Santamaría *et al.* 1987). Double-pass systems are based on recording images from a point-source object after reflection on the retina and a double pass through the ocular media. In contrast to wave front aberrometry, the double-pass systems directly compute the modulation transfer function from the acquired double-pass retinal image by Fourier transformation, allowing the complete characterization of the optical quality of the eye, mainly degraded by higher-order ocular aberrations and scattered light. Because of the differences between both technologies, recent studies suggest that wavefront aberrometers may overestimate retinal image quality in eyes where higher-order aberrations and scattered light are prominent (Díaz *et al.* 2006).

6.8.5.2 Impression cytology (for HLA-DR)

Samples for impression cytology for HLA-DR will be taken in the right eye (only if right eye is eligible) and only in patients with severe Dry Eye, at Baseline visit (Day 1) and Day 84 (Visit 5) or premature withdrawal, using the **EYEPRIM™** sterile medical device.

For sensitive patients, it may be wise to practice a topical anesthesia of the eye. In this case, the anesthesia must be done at Day 1 and Day 84.

Severe Dry Eye is defined as an OSDI score ≥33 and/or Corneal Fluorescein Staining ≥3 at baseline visit (Day 1).

HLA-DR will be assessed by flow cytometry and expression will be quantified in arbitrary units of fluorescence (AUF) and percentage of conjunctival cell expressing HLA-DR by a central lab.

If the sample taken at baseline is uninterpretable, the sample at Day 84 will not be taken. Furthermore, if a patient discontinues the study before Day 84, a sample will be taken at the discontinuation visit if the baseline sample was interpretable.

One of the most important biological risk concerning cytology impression samples, is the prion disease.
There is no actual way to eliminate the biological risk itself. One way to reduce it is to add a screening form such as the following one:
• Have you received a growth hormon treatment before 1988?
• Is any member of your family (parents, brother/sister) infected by Creutzfeldt-Jakob disease?
• Did you undergo brain or spinal cord surgery before 1995?
If the patient answer yes to one of the questions, the investigator should proceed to a more thorough interrogation in order to decide if the patient is at risk.

6.9 Monitoring plan

Monitoring will be performed according to the monitoring plan implemented by the Contract Research Organization (CRO) in charge of clinical research activities.

To ensure monitors can perform their monitoring activities at each visit, the Investigator and his/her investigation site staff agrees to allocate sufficient time with investigational site staff and to grant the Sponsor or its representative direct access to all investigation-related facilities and source data/documents. In addition, the Investigator agrees to allow monitoring visits at the frequency and duration described in the monitoring plan.

The monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the CIP, GCP (ISO 14155) and the applicable regulatory requirements. To ensure accurate, complete, and reliable data, the Sponsor or its representative will perform the following activities:

- Provide instructional material to the investigational sites, as appropriate;
- Provide start-up training and continuing training (if applicable) to the Investigators and investigational site staff on the CIP, the completion of the e-CRF, and procedures;
- Make periodic monitoring visits (as defined in the monitoring plan) to the investigational site to:
  - Monitor the patient data recorded in the e-CRF against source documents,
  - Assess rights, safety and well-being of patients,
  - Provide information and support to the Investigator(s),
  - Confirm the facilities and investigational site staff remain acceptable since previous visit,
  - Ensure that activities are conducted according to GCP (IS014155) requirements and the CIP including verifying the accuracy of data recorded in the e-CRF
  - Ensure that IMD accountability checks are being performed;

- Be available for site staff and stay in contact with the investigational site staff by mail, telephone, electronic mail, and/or fax;
- Review and evaluate e-CRF data and use queries to document errors in data collection and forward them to the Investigator for resolution.

The Investigator(s) and site staff involved in the investigation should be available during monitoring visits for:

- Medical questions concerning patients safety;
- Verification of data from source documentation;
- Possible e-CRF corrections and queries resolution;
- IMD / non-IMD-related questions.

Following each monitoring visit, the Investigator(s) will be sent a follow-up letter detailing any actions required by either the investigational site staff or the site monitor. Any actions must, wherever possible, be addressed immediately, or by the next scheduled monitoring visit. The letter must summarize:

- All major issues confirmed as resolved during the visit;
- Any unresolved issue observed (new or not) and specific action required with deadline of resolution;
- A protocol deviation synthesis.

This letter should clearly state the information discussed with the investigational staff at the site. It must also point out any unresolved issue or recurrent issues which may deal with a Non Conformity registration and sponsor involvement due to regulatory discrepancies.

6.9.1 Source documents

Each participating investigational site will maintain appropriate medical and research records in compliance with ISO14155 and any other regulatory and institutional requirements for the protection of patient's confidentiality.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the investigation. Source data are contained in source documents.

Source documents are any original documents, data and records. These may include, but are not limited to, patient medical records, hospital charts if any, clinic charts, laboratory notes, patient's questionnaires, patient's diaries if any, the Investigator's patient investigation files, pharmacy dispensing records and recorded data from automated instruments.

Some specific medical data gathered during routine medical practice visits prior to the participation can be used in selection visit and before informed consent form on the patient best care interest.

6.9.2 Source data verification

One of the primary responsibilities of monitoring is to verify that the reported data in e-CRF are accurate, legible and verifiable from source documents and any other source data.

Source data verification (SDV) will be performed in e-CRF of all patients and SAE/pregnancy related documents, consisting in a comparison of the source documentation and other records relevant to the investigation with the e-CRF. This will require direct access to all original records of each patient.

It will be verified that informed consent documentation is filed for all screened patients whether or not they were randomised into the investigation and that the information is listed in the source documents.

The SDV will ensure the data are Attributable, Legible, Contemporaneous, Original and Accurate (ALCOA guiding principles).

6.9.3 Case report forms

The patients will be monitored throughout the investigation and all results of evaluations will be recorded in an electronic data capture system (e-CRF).

The e-CRF completion guidelines will be provided and reviewed with the study staff before the start of the investigation.

The investigator and authorised study staff will have secured access to enter the data in the appropriate sections of the e-CRF.

e-CRF must be completed for each patient screened in the investigation, including screening failure patients. It should be completed as soon as possible after the patient visit.

The Investigator and authorized investigational staff will ensure that proper data for the clinical investigation are collected and accurately documented in the appropriate sections of the e-CRF.

The Investigator will be responsible for the punctuality, completeness, consistency and accuracy of e-CRF. e-CRF and source data will be retained by the Investigator for data verification at each scheduled monitoring visit.

An investigator who has signed the protocol should personally sign the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely.

All information recorded on the e-CRFs for this study must be consistent with the patients' source documentation (*i.e.*, medical records).

Monitoring procedures developed by Laboratoires Théa/CRO will be followed in order to comply with ISO 14155 (GCP guideline) and the Code de la Santé Publique (CSP). On-site checking of the e-CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

This will require direct access to all source documents, any original documents, data, and records of each patient.

The investigator(s) and site staff involved in the study should be available during monitoring visits for:

- Medical questions concerning patients safety;
- Verification of data from source documentation;
- Possible e-CRFs corrections and queries resolution ;
- IMDs/non IMDs questions.

A copy of completed e-CRF pages, SAE / Pregnancy will be stored in the Investigator's archives for at least 15 years after completion or discontinuation of the trial.

7 STATISTICAL CONSIDERATIONS

7.1 Statistical design, method and analytical procedures

The statistical analysis will be performed under the responsibility of Laboratoires Théa by the CRO in charge of statistics according to the Statistical Analysis Plan that will be based on the protocol and finalised before unblinding.

7.2 Definition of investigation sets

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 Blind Review Meeting.

Safety population will be composed of all patients exposed to the investigation drug, i.e. having used at least one administration of the investigation drug.

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.

For patients with both eligible eyes, 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.

For patients with one eligible eye, the “worst eye” will be the eligible eye.

7.3 Statistical analyses

Statistical analysis will be performed on SAS version 9.4 (or later).

A detailed statistical analysis plan will be written and approved before any analysis.

The type one error (α) will be set at 5 %.

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

Continuous variables will be summarised by number of non-missing observations, number of missing observations, mean, and standard deviation, median, Q1-Q3, minimum and maximum.
Categorical data will be summarized by frequency and percentage of patients in each category.
Percentages will be based on non-missing observations.
95% Confidence Intervals might be presented.

All tables will be presented results by treatment group. In case of parameters measured on both eyes, results will be presented separately.

For primary analysis performed on FAS, LOCF method will be applied in case of missing value.

7.3.1 Descriptive analysis (FAS)

Demographic data (selection visit) will be described overall and by treatment group.

Medical and surgical history (ocular and systemic) will be described by SOC and PT.

Previous and concomitant treatment will be described by ATC names (level 3 and 4).

Other parameters will be described and analysed in further part.

7.3.2 Primary performance variable

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 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, will be computed for the difference of T2259 minus Vismed® Multi. If the upper bound is no higher than two 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 non-inferiority analysis will be provided primarily in the PP population then confirmed in the FAS population.

On FAS population, analysis will be performed firstly with imputation of values in case of missing data with LOCF technique (D8 value or value in case of withdrawal) and secondarily, without imputation (observed cases).

For the primary performance endpoint, the investigator site and the investigation product-by-investigator site interaction will be explored as a secondary analysis prior to presenting the final model.

Descriptive tables will be produced presenting baseline data, D8, D35 data and D84 and change from baseline.

7.3.3 Secondary performance variables

Secondary performance endpoints analysis will be provided in the PP population and the FAS population.

Same analysis (ANCOVA constructed using main effects of investigation product and baseline score as covariate and descriptive analysis) will be performed on each parameter presented below:

- Change from baseline in Oxford total score 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 OSDI (Ocular Surface Disease Index) total score at Day 8, Day 35 and Day 84;
- Change from baseline in DEQ-5 total score at Day 35 and Day 84;
- Change from baseline in Van Bijsterveld score* (lissamine green staining) total 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.

For conjunctival hyperaemia* using McMonnies photographic scale at Day 8, Day 35 and Day 84, treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test based on modified ridit scores, stratified by the baseline value.

Each Dry Eye symptom at Day 8, aDay 35 and Day 84 will be described and compared between treatment group using percentage of patient with an improvement, a stability or a degradation using a chi-2 test.
The total score for the 7 predefined symptoms will be compared between treatment groups using ANCOVA (model from the main analysis).

Performance assessment by the investigator at Day 35 and Day 84 will be described by treatment group. An additional description will be provided in 2 classes (Very satisfactory or satisfactory, not very satisfactory or unsatisfactory) and compared between groups using a Wilcoxon signed-rank test.

Analysis for others parameters will be specified in Statistical Analysis Plan (SAP)

7.3.4 Safety endpoints

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

Descriptive tables will be produced for each ocular symptom upon instillation at Day 8, Day 35 and Day 84, by treatment group. The total score for the 7 predefined symptoms will be compared between treatment groups using ANCOVA (model from the main analysis):

- Far best-corrected visual acuity (in logMAR) at Day 84 will be analysed descriptively. The frequency distribution will be also presented in /10 (1/10, 2/10 to 10/10, >10/10);

- Tolerance assessment by the investigator at Day 35 and Day 84 will be described by treatment group. An additional description will be provided in 2 classes (Very satisfactory or satisfactory, not very satisfactory or unsatisfactory) and compared between groups using a Wilcoxon signed-rank test.

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

- All TEAEs;
- Ocular TEAEs (localisation = Right eye, Left eye or Both eyes);
- Non-ocular TEAEs (localisation = Other);
- Treatment-related TEAEs;
- Serious TEAEs;
- TEAEs leading to drug withdrawal.

An Individual data listing, will be presented for each patient Diagnosis (verbatim) all the recorded variables, MedDRA SOC and PT, duration and time from Day1.

7.4 Interim analysis

No interim analysis is planned.

7.5 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.

8 DATA MANAGEMENT

8.1 Data collection and handling

The Investigator should provide the Sponsor with complete test results and all data derived from the investigation. Only the Sponsor may make information obtained during the investigation available to physicians or regulatory agencies, except as required by regulation.

8.2 Electronic Case report form (e-CRF)

Entries in e-CRF shall be made complete and correct.

All data entry and modifications will be stored in an audit's trail.

Diagnosis for Adverse events and medical history will be coded using MedDRA. Whodrug ATC code will be used for concomitants treatment coding. Versioning will be specified in the Data Management Plan.

Data Management activities will be performed by the CRO in charge of Data Management.

8.3 Monitoring / data audits

Laboratoires Théa/representatives of Laboratoires Théa shall be permitted to audit any proposed investigational site prior to commencement and during the course of the investigation to satisfy itself that the investigational site is suitable and has the necessary facilities, staff and capacity for the conduct of the investigation. The investigator will ensure that his/her centre has the necessary facilities, time and staff for the conduct of the investigation, and that these will be maintained for the duration of the investigation. The investigator will cooperate with Laboratoires Théa and any person nominated by Laboratoires Théa to monitor or supervise the conduct of the investigation.

The investigation may be inspected by the competent authority. In case of an audit, the investigator will be informed in advance.

The electronic data capture system is to be made available for review by the clinical monitor or auditor or inspectors. The investigator is required to give **access to all source documents** and investigation data. Laboratoires Théa and CROs will not require the investigator or any member of their staff to take any action or be a party to any action which is contrary to the laws of the country in which the investigation is being carried out or to medical ethics.

8.4 Confidentiality

In accordance with GCP and with the national data protection laws, all information concerning the subjects will be treated as strictly confidential by all persons involved in the investigation including the clinical, medical and statistical monitor.

The investigator acknowledges that any information acquired from Laboratoires Théa (and CROs) or developed or acquired in connection with the investigation are strictly confidential and that he will not disclose the same to any third party nor use the same for any purpose without first obtaining the consent of Laboratoires Théa in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his site, but only so far as required for the purposes of the investigation, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

8.5 Archiving

The investigator must retain the subject identification codes for at least **15 years** after completion or discontinuation of the investigation. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years, to meet national requirements. The investigator must produce them or supply copies thereof to Laboratoires Théa (or CROs), or to the regulatory authorities upon demand, whilst ensuring subject confidentiality at all times.

8.6 Investigation commencement and discontinuation

Before the investigation starts, the clinical monitor must ensure that all relevant documents are available and that ANSM authorisation and CPP approval have been obtained. Only then, arrangements for shipment of the clinical supplies can be made and start of recruitment can begin.

In addition to the right to terminate the investigation agreement (see below), Laboratoires Théa shall have the right to terminate the investigation at any time upon written notice to the investigator. Without limiting this right, Laboratoires Théa would only terminate the investigation in the following circumstances:

- If medication serious breach in human or animal studies should indicate discontinuation of the investigation;
- If Laboratoires Théa should wish to discontinue the investigation for commercial reasons;
- If Laboratoires Théa has reason to believe that the investigation cannot be satisfactorily completed, including, but not limited to, inadequate number of subjects enrolled or insufficient centres recruited within the necessary time.

9 AMENDMENTS TO THE CIP

By signing the CIP, the investigator confirms that he/she agrees to perform the investigation as outlined in the CIP.

The CIP is the binding document for the investigator, the sponsor and its designee; modifications are only valid if agreed upon by the sponsor, its designee and the coordinating investigator. Modifications must be documented in a signed amended CIP.

The sponsor will promptly report the following for review or information to the Ethics Committee(s) and the Competent Authority for:

- Substantial CIP modifications;
- Administrative changes;
- Deviations to the CIP implemented to eliminate immediate hazards to the trial patients;
- New information that may affect adversely the safety of the patients or the conduct of the trial. The EC and the Competent Authority must be informed and approve all CIP amendments, in accordance with local legal requirements before implementation. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The written signed approval of the CIP amendment must contain specific identification of the document (e.g., the investigator's name and the protocol title and number).

10 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The investigator will conduct the investigation in accordance with this CIP, all relevant local laws, regulations or guidelines and in accordance with the principles of GCP. The investigator should not initiate the investigation before:

- The CIP is signed;
- Written approval from the appropriate IEC and Clinical Trial Authorization from Competent Authority are received;
- The site is initiated by Laboratoires Théa or the CRO designated by Laboratoires Théa.

During the investigation, in case of important deviations observed in an investigational site (such as deviations related to inclusion and/or exclusion criteria, deviations that may put a patient at risk), the sponsor could decide to stop the enrolment in this site.

At the end of the investigation, CIP deviations will be reviewed and classified as minor or major during a blind data review meeting that will be held before database lock. The exclusion of patients from the analysis sets (see details of analysis sets in Section 7.2) will be discussed during the blind data review meeting.

11 IMD ACCOUNTABILITY

IMD are to be dispensed only by the Investigator, and will be used in accordance with this CIP.

Patients will be instructed to keep all used and unused IMD and to return them upon request.

All administrations and returns of IMD (used, partially used and unused) have to be documented and must be accounted for on the IMDs Accountability Log provided. The overall accountability must be documented and reviewed. A reconciliation of the initial inventory and the final returns must be undertaken..

All IMD will be retained for inspection by the monitor who will check the completion of the Study Drug Form (SDF). The SDF should be completed by the Investigator and/or the pharmacist and verified by the monitor. Compliance will be assessed using the IMD Accountability Log and questions raised to the patient.

Collected used/unused/broken bottles of the supplied IMD will be returned to the clinical supplies distributor for destruction and cannot be used for any other patient.

12 STATEMENTS OF COMPLIANCE

This investigation will be conducted in accordance with the ethical principles of the Declaration of Helsinki of October 2013, with GCP as described in the International Standards ISO 14155 and with the local regulations.

Prior to commencement of the investigation, the Sponsor or his legal representative in the community must submit a valid application, with the same version of the documentation, to the IEC and the Competent Authority.

The Sponsor or his legal representative will report any amendments (see Section 9, page 68) and safety-related events (see Section **14** page 73) according to the local regulations.

The end of investigation will be notified to the IEC and the Competent Authority in accordance with the local regulations. If the investigation has terminated prematurely, the reason for the termination must be given.

The sponsor holds and will maintain an adequate insurance policy covering damages arising out of Laboratoires Théa sponsored clinical research studies. When required, a hospital specific indemnity agreement will be used.

13 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the International Standards ISO 14155 on GCP for medical devices and the requirements in the Declaration of Helsinki.

Prior to any investigation-related activity, the Investigator or designated person must give the patient (or the patient's legally authorized representative) oral and written information about the aims, methods, anticipated benefits, potential risks and inconveniences of the investigation. The measures taken to safeguard the patient's privacy and the protection of personnel data should also be described in the informed consent.

The patients must be informed about their right to abstain from participating in the investigation and to withdraw their consent at any time without affecting their medical care. The patient (and/or the legally acceptable representative) must be given the opportunity to ask questions, and have reasonable time for reflection before giving his/her informed consent.

If the patient is illiterate, oral information regarding the investigation will be provided to the patient using the informed consent form (ICF). A witness will be present during the entire informed consent discussion. The witness will personally sign and date the ICF to confirm that the information was accurately explained to the patient, and apparently understood, and that consent was freely given.

Two copies of the ICF shall be signed and dated by the patient (or the legally authorized representative) and the Investigator prior to initiate any investigation related procedures. One original consent form will be given to the patient and the other original will be included in the Investigator's investigation file.

The information/consent form may be revised during the investigation whenever important new information becomes available. The amended ICF will be submitted for approval to the IEC and/or Competent Authorities as appropriate (see Section 9, page 68). Once approved, informed consent of the already enrolled patients will be documented as described above i.e., in the same way as the initial informed consent.

14 Materiovigilance / Serious Adverse Event reporting

14.1 Definitions

14.1.1 Definition of adverse event (AE) and adverse device effect (ADE)

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Adverse device effect (ADE) is an AE **related** to the use of an investigational medical device. This definition includes:

- AEs resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device (IMD);
- Any event resulting from a use error or from intentional abnormal use of the IMD.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the e-CRF. Concomitant illnesses, which existed prior to entry into the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the e-CRF.

14.1.2 Definition of a Serious Adverse Event (SAE) or Serious Adverse Device effect (SADE)

A **serious adverse event or a serious adverse device effect** is an adverse event or adverse device effect that results in:

- ✓ Death of the patient;
- ✓ The condition of the patient is life-threatening;
- ✓ The patient requires hospitalisation, or a prolongation of existing hospitalisation;
- ✓ Persistent or significant disability or incapacity;
- ✓ A congenital anomaly or birth defect;
- ✓ Other medically-important events.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE.

14.1.3 Definition of the severity of an Adverse Event

The intensity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the e-CRF:

1 = MILD : Event results in mild or transient discomfort, not requiring intervention or treatment and does not interfere with the patient daily activities;

2 = MODERATE : Event results in sufficient discomfort, may require an additional treatment, but does not interfere with the patient's daily activities;

3 = SEVERE: Event results in significant symptoms, may require an additional treatment, or a modification of this treatment (or hospitalisation) and may interfere with the patient's daily activities.

Caution: The term "severe" is used to describe the intensity (severity) of the event. This means it is not the same as "serious" used to describe the seriousness of serious adverse event (SAE) which is based on

patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (see section 14.1.2 for having the definition of a SAE).

14.1.4 Relationship with the Investigational Medical Device

The investigator will assess the causality/relationship between the IMD and the AE and record that assessment in the e-CRF based on the following definitions (only one answer possible):

1 RELATED: The adverse event is related to the IMD and cannot be reasonably explained by others factor (e.g., concomitant therapy, patient condition, and/or other intervention);

2 NOT RELATED: A simultaneous disease, a simultaneous treatment or any other known cause is clearly responsible for the adverse event.

14.1.5 Recording of Adverse Events

The investigator shall:

a) Record in the e-CRF any **adverse event**, together with an assessment. Adverse event reporting will extend from signing of informed consent until the patient final study visit;

b) Report to the sponsor, without unjustified delay, all serious adverse events; this information shall be promptly followed by detailed written reports;

c) Supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

14.2 Recording of AEs or ADEs

All AEs or ADEs regardless of severity occurring between signature of the informed consent form and the last visit of the patient must be recorded on the AE form provided with the e-CRF. This will include the following minimal information:

-Description of the AE or ADEs (diagnosis, localisation…)

-Intensity of symptoms (severity)

-Seriousness of the Adverse event

-Action taken for AE

-Assessment of relationship with the investigational

product/device or protocol procedure

-Outcome

If there is a worsening of a medical condition that was present before starting the clinical investigation, this should be considered as a new AE and a complete evaluation should be recorded.

14.3 Reportable event:

In case of Serious Adverse Event, the Investigator must:

1. Complete the paper SAE form with all available initial information.
2. Immediately scan and send out the completed SAE form to the **trialsafety@theapharma.com** whilst copying the field CRA of the CRO.

   If it's not possible, please fax this SAE form over to**: +33 4 73 98 14 24**

3. **Within 24 hours**, send the completed original SAE form duly completed to the following address by mail:

   Laboratoires Théa
   GlobalSafety and MedInfo Department
   12,rue Louis Blériot
   F-63017 CLERMONT-FERRAND Cedex 2

   The initial report must be as accurate as possible, including details of the current illness, an assessment of the causal relationship between the event and the IMD. Additional follow-up reports, must be send back to Laboratoires Théa within 24 hours upon receipt of follow-up information query.
   In addition, the following information have to be recorded in the appropriate sections of the e-CRF:
   - Demography
   - Medical and surgical history
   - Previous and concomitant medication
   - Investigational medication administration record

The Investigator is responsible for ensuring the follow-up of any patient who experiences a SAE during the investigation. The Investigator or an appropriate qualified physician must re-examine the patient at regular intervals until completion of the Last Patient Last Visit. Further follow up information will be reported to Laboratoires THÉA.
As for all other investigation documents, the Investigator will retain a copy of the SAE form for 15 years.

Laboratoires Théa must report to the NCAs where the clinical investigation has commenced:

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and hat requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after

Note: Member States may also require separate reporting to the independent ethics committee(s) (IEC) and/or separate reporting to the other clinical investigators/ centers involved in the clinical investigation.

- any other reportable events or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

If the investigator is aware about any SAE occurring **within 1 month after the end of the clinical investigation** and that he considers that it is be related to the IMD, the SADE should be reported..
After consultation with Laboratoires THÉA, the Investigator may be required to provide information about certain SAE to the IEC according to the institutional policy.

Process for reporting a pregnancy

This is the same process as serious adverse event reporting.
The occurrence of a pregnancy (reported or diagnosed) must be reported by the Investigator to the Sponsor as an SAE from the signature of the informed consent form, within 24 hours.

15 VULNERABLE POPULATION

This clinical investigation will not be conducted in children, or in any other vulnerable populations.

If the patient is not capable of giving consent, the written consent of the patient's legal representative will be required before participation in the investigation (see Section 13, page 70).

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Sponsor may suspend or prematurely terminate the clinical investigation for any safety, ethical or administrative reason at any time. The Investigator, IEC or Competent Authority may suspend or prematurely terminate participation at the investigational sites for which they are responsible.

If the investigation is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators/institutions, the IEC and the Competent Authority of the termination or suspension with the reason(s) for the termination or suspension, as per the applicable regulatory requirement(s).

If the suspension or premature termination is in the interest of safety, the Sponsor shall inform all other principal Investigators.

17 PUBLICATION POLICY

The data resulting from this investigation will be the proprietary information of Sponsor. None of the data resulting from this investigation will be allowed to be presented or published in any form, by the Investigator or any other person, without the prior approval of Sponsor.

At the end of the investigation, a clinical investigation report will be written by the Sponsor. The draft reports will be discussed with the coordinating Investigator and with the Sponsor.

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19 APPENDICES

19.1 Appendix I: T2259 Leaflet

LEAFLET:


Read the instruction manual

THEALOZ DUO FORTE

Enhance protection, hydration and lubrication of the eye for treatment of moderate to severe dry eye syndrome associated with superficial keratitis.
ABAK Bottle - Preservative free.

COMPOSITION:
Trehalose ……6.00 g
Sodium hyaluronate ……0.20 g
Sodium Chloride, Trometamol, Hydrochloric acid, Water for injections….to 100 ml

NAME AND ADDRESS OF MANUFACTURER:


Laboratoires THEA – 12 rue Louis Blériot - 63017 Clermont-Ferrand – Cedex 2 – France

WHEN TO USE THEALOZ DUO FORTE:

THEALOZ DUO FORTE contains a solution for administration into the conjunctival cul-de-sac of the eye and can be used with contact lenses. THEALOZ DUO FORTE can be used when you have discomfort, stinging, irritated, red, watery eyes, that are sensitive to bright light, bloodshot or when you have the foreign body sensation. These symptoms can be caused by external factors such as wind, smoke, pollution, dust, sunny or cold conditions, dry heat, air conditioning, plane journeys, and prolonged use of visual display terminal.

THEALOZ DUO FORTE is preservative-free which helps provide good levels of tolerance on the eye. The solution can be used by contact lens wearers who wear any type of contact lens and it provides immediate comfort that lasts all day long.

PROPERTIES:
THEALOZ DUO FORTE is a sterile, preservative free, isotonic and pH neutral aqueous ophthalmic solution. Its main ingredients are trehalose, a disaccharide present in many plants

and animals, and sodium hyaluronate, a polysaccharide naturally present in the eye.

Trehalose protects and hydrates. For these reasons, it is essential in the anhydrobiotic process used in certain tiny organisms (a slow metabolism that helps them live in dry conditions). Trehalose protects and stabilises membranes and proteins of the cells exposed to damaging conditions like in the absence of water.

Sodium hyaluronate is natural polysaccharide found in the human eye with proven benefits to hydrate and lubricate the surface of the eye. It keeps the solution on the eye's surface giving long lasting relief and cutting down the healing time of the corneal epithelium (the clear surface on the eye).

The innovative combination of Trehalose and Sodium hyaluronate in THEALOZ DUO FORTE protects, hydrates and lubricates the eye surface for a long time and with a maximum comfort.

THEALOZ DUO FORTE is supplied in the ABAK multi-dose bottle to avoid the use of chemical preservatives. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution. The solution is protected and can be used for up to 2 months after the bottle is opened.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:
- Do not use if you are allergic to any of the ingredients.
- Do not touch the surface of the eye with the tip of the bottle.
- Do not inject, do not swallow.
- If the safety ring is damaged, do not use the product.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

INTERACTIONS:
Wait at least 10 minutes between using two different eye products

HOW TO USE THIS PRODUCT:

METHOD AND ROUTE OF ADMINISTRATION:
USE ONLY IN THE EYE.
- Wash hands well before use,
- Do not touch the eyes or eyelids with the tip of the bottle, especially when you think you may have an eye infection,
- Drop one drop in the lower conjunctival sac (the space between the eye and eyelid), while gently pulling the lower lid downwards and looking up.
- Put the cap back after use.

DOSAGE:
1 drop in each eye, 2 to 4 times daily.
THEALOZ DUO FORTE can be used when wearing contact lenses.

SIDE EFFECTS:
You may have mild eye irritation and ocular hyperaemia, although this is very unusual.

STORAGE OF THE PRODUCT:
Do not keep an open bottle for more than 2 months.

Store below 25°C

DO NOT USE AFTER THE EXPIRY DATE CLEARLY MARKED ON THE OUTER CARTON. The expiry date refers to the product in intact packaging, stored correctly. Do not use the bottle if it is damaged.

INSTRUCTIONS UPDATED: 10/2018.

Manufacturer

Store below 25°C

Do not use if package is damaged

Sterilised using aseptic processing techniques

Consult instructions for use

Caution

Use-by date

Batch number

19.2 Appendix II: Vismed® Multi leaflet

VISMED® MULTI

LUBRICANT EYE DROPS

Instruction leaflet

VISMED® MULTI
0.18% sodium hyaluronate obtained through fermentation.
Lubricant eye drops.
Sterile, preservative-free.

Composition:
1 ml of solution contains 1.8 mg sodium hyaluronate, sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride and purified water. The solution is hypotonic.

Indications:
Moderate and severe sensations of ocular dryness.

Contraindications:
Hypersensitivity to one of the ingredients of the product.

Interactions:
Do not administer VISMED® MULTI at the same time as other eye medication or products as it could change the effects.

Side effects:
In rare cases, temporary effects, such as irritation of the conjunctiva, sensation of something in the eye, redness or a burning sensation, as well as momentary blurred vision can occur.

Dosage and method of administration:
Remove the security band before first use. Take off the protective cap. Tilt your head backwards and position the tip of the bottle above the eye to be treated. Pull the bottom eyelid downwards with your index finger. Squeeze the body of the bottle and one drop of VISMED® MULTI will be released easily (see illustrations). Unless recommended otherwise, place 1 to 2 drops of VISMED® MULTI into the eye as often as needed. Blinking several times will ensure a transparent and durable film of the solution is spread evenly across the surface of the eye. VISMED® MULTI can be used while wearing contact lenses (soft and hard).

Precautions:
To not touch the tip of the bottle and do not touch the surface of the eye with the tip of the bottle. Replace the protective cap on the VISMED® MULTI bottle after use. Do not use VISMED® MULTI if the bottle is damaged. After the first use, VISMED® MULTI can be used for up to 6 months. After opening, dispose of any unused solution after 6 months. After this time, sterility cannot be assured and this may be associated with a risk of infection.
Store below 30°C. Do not freeze. Do not use VISMED® MULTI after the expiry date mentioned on the bottle and box. If your condition persists while using VISMED® MULTI, see a doctor. Keep out of the reach of children.

Properties and mechanism of action:
VISMED® MULTI contains sodium hyaluronate, a natural polymer that is also present in the structures of the human eye. The specific physical characteristics of sodium hyaluronate give VISMED® MULTI its viscoelastic and water retaining properties. Therefore, VISMED® MULTI forms a stable film on the surface of the eye, which is very slowly dispersed through blinking. VISMED® MULTI combines a long-lasting effect with maximum comfort. Due to its specific composition, VISMED® MULTI is very well tolerated.
VISMED® MULTI does not contain any preservatives.

Presentation: 15 ml of solution in a multi-dose bottle. Last revision: 2018-01

Instructions for use on the back.

Horus PHARMA

Distributor:
Horus Pharma – 148 Avenue G. Guynemer
06700 Saint-Laurent du Var – France
Tel: 04 93 19 54 03, www.horus-pharma.fr
15 ml – ACL Code: 3664490000031

TRB CHEMEDICA OPHTHALMIC LINE

TRB CHEMEDICA AG
Otto-Lilienthal-Ring 26
85622 Feldkirchen/Munich – Germany

CE 0123

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VISMED® MULTI

LOT

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