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

Protocol number:	**LT2769-001/ 17E1044**
Unique National Number:	**TN2017-NAT-IND-8**
Investigational Product:	**T2769**
Form:	**Solution**
Administration route	**Ocular**
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Date and Protocol version:	Final Version 2.0 of 13/11/2017

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1 GENERAL INFORMATION

PROTOCOL #: LT2769-001/ 17E1044

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PROTOCOL TITLE:

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

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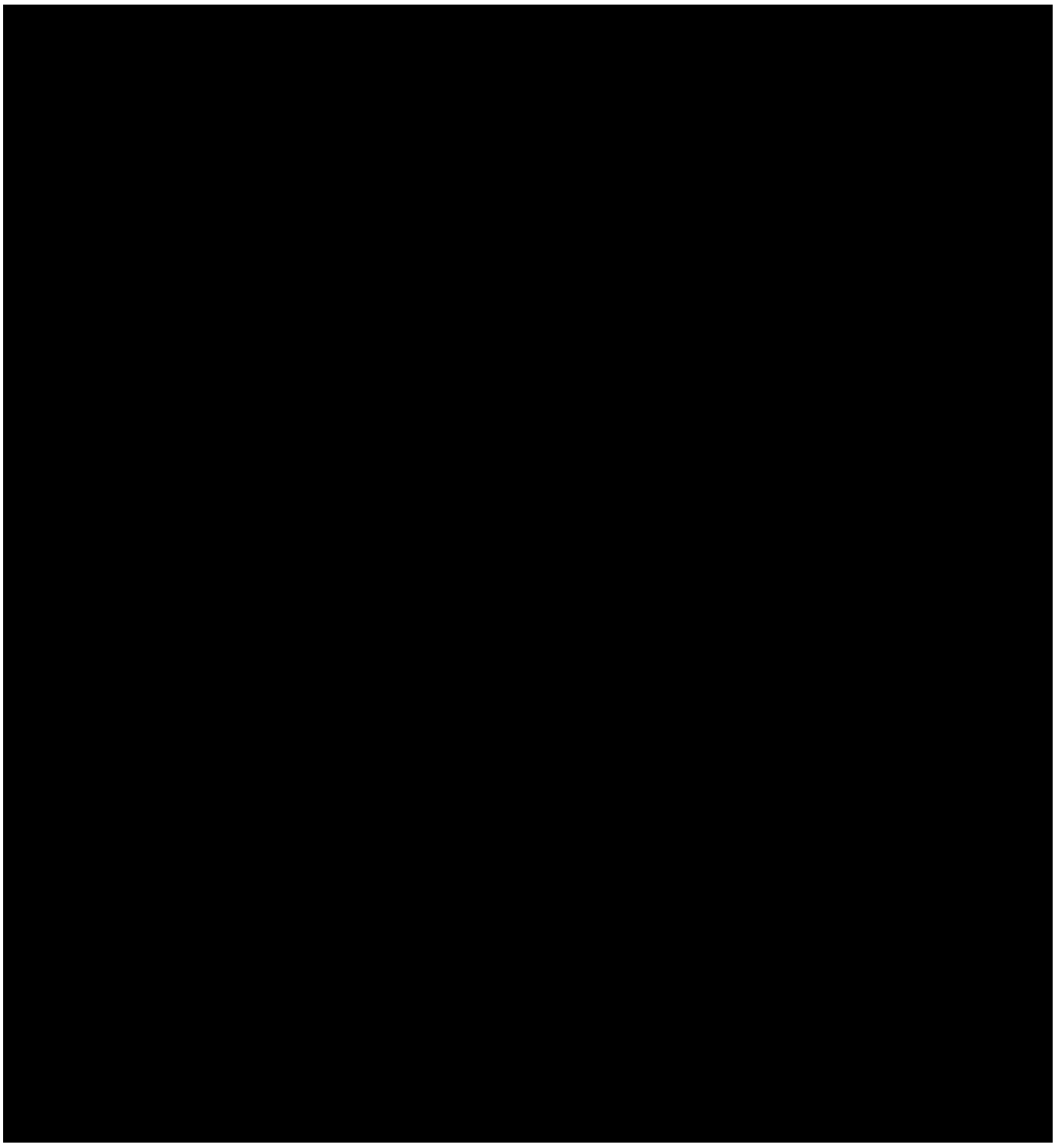


ABBREVIATIONS LIST:

AE	Adverse Event
AFAQ	Association Française pour l'Assurance de la Qualité
BOCF	Baseline Observation Carried Forward
CA	Competent authorities
CPP	Comité de Protection des Personnes
CRA	Clinical Research Assistant
CRF	Case Report Form
D	Day
DCF	Data Clarification Form
DED	Dry Eye Disease
DEWS	Dry Eye WorkShop
EC	Ethic Committee
FBCVA	Far Best Corrected Visual Acuity
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
ITT	Intent to Treat
IP	Investigational Product
LOCF	Last Observation Carry Forward
MEdDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified Intent to Treat
OSDI	Ocular Surface Disease Index
P	Period
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBUT	Tear Break-Up Time
VAS	Visual Analog Scale

2 SYNOPSIS OF THE PROTOCOL

Unique National Number	**TN2017-NAT-IND-8**
Protocol number:	**LT2769-001/ 17E1044**
Title	**Efficacy and Safety Assessment of T2769 in patients with moderate to severe Dry Eye Syndrome**
Sponsor	Laboratoires THEA
Principal Investigator	[redacted]
Study Centre(s)	Multicentre study in Tunisia
Planned schedule	Submission: July 2017 Planned initiation: September 2017 Planned completion of clinical phase: May 2018
Primary Study Objective	To assess the efficacy of T2769 in patients with moderate to severe Dry Eye Syndrome.
Secondary Study Objective	To assess the safety of T2769.
Primary Efficacy criterion	Evolution of the ocular symptomatology on a Visual Analog Scale (VAS) between (D1) and after 42 days of treatment (D42).
Secondary Efficacy criteria	• Evolution of global ocular staining score according to Oxford 0-15 grading scheme (fluorescein coloration) between D1 and after 42 days of treatment (D42). • Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and after 42 days of treatment (D42). • Evolution of the soothing sensation assessed by the patient between D1 and after 42 days of treatment (D42).
Other evaluation parameters	**<u>Other assessment at D14</u>** • Evolution of the ocular symptomatology on a Visual Analog Scale (VAS) between D1 and after 14 days of treatment (Day 14). • Evolution of global ocular staining score according to Oxford 0-15 grading scheme (fluorescein coloration) between D1 and after 14 days of treatment (D14).

- Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and after 14 days of treatment (D14).
- Evolution of the soothing sensation assessed by the patient between D1and after 14 days of treatment (D14).

Other assessment at D14 and D42

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

Safety criteria

After 14 days and 42 days of treatment with the T2769:

- Ocular symptoms upon instillation: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, and other symptoms will be graded by the patient.

After 42 days of treatment with the T2769

- Far best corrected visual acuity assessment.
- Ocular tolerance assessment by the investigator.
- Ocular tolerance assessment by the patient.

During the 42 days of treatment with T2769:

- Ocular and systemic adverse events (AE)

Patient number	At least 55 enrolled patients for at least 50 evaluable patients
Study Design	Multicenter study, open.
Study duration	Run-in period with preservative free artificial tears (NaCl 0.9%) : from D-14/D-10 to inclusion visit (D1) Dose regimen: One drop in each eye 3 to 6 times per day. Treatment period: 42 ± 5 days. Total study duration: maximum of 61 days.
Investigational product	T2769 (Hyaluronic acid 0.15%, Trealose 3%, Naaga 2.45%. pH 7.2. ABAK vial). Dose regimen for 42 days: one drop in each eye 3 to 6 times daily.
Study Visits	Visit#1: Screening visit Day -14/D-10. Visit#2: Day 1. Visit#3: Day 14 (+/- 1 day). Final Visit: Day 42 (+/-5 days). ***Visits should be performed at the same hour (± 2 hours)***
Inclusion Criteria	*Criteria at the screening visit* 1.1. Informed consent signed and dated. 1.2. Man or Woman aged ≥ 18 years. 1.3. Known Dry Eye Syndrome requiring artificial tears within the last 3 months prior to study screening.
	Criteria at the inclusion visit 1.4. Patient having used only preservative free artificial tears (Physiol®) as ocular medication during the run-in period (from D-14/D-10 to D1). 1.5. No ocular instillation at least 2 hours prior to the inclusion visit. 1.6. Patient having at least one *Eligible Eye*, defined by both following conditions: ➢ Global 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 1.7. Conjunctival hyperaemia: Score ≥ 1 and ≤ 3 (Mc Monnies scale) 1.8. At least one ocular symptom: itching/pruritus; burning/irritation; light sensitivity with a severity score ≥ 1 and ≤ 3 for each symptom, 1.9. Diagnosis of moderate to severe dry eye syndrome defined by OSDI Score ≥ 18.
Exclusion Criteria	2.1 Ophthalmic Exclusion Criteria in at least one eye 2.1.1 Best far corrected visual acuity ≤ 2/10 2.1.2 Severe blepharitis 2.1.3 Severe Dry Eye associated to: ➢ Ocular Rosacea ➢ Progressive Pterygium ➢ Eyelid malposition ➢ Corneal dystrophy ➢ Ocular neoplasia ➢ Filamentous keratitis ➢ Corneal neovascularisation ➢ Orbital radiotherapy 2.1.4 History of severe ocular traumatism, ocular infection or ocular inflammation within the last 6 months. 2.1.5 History of ocular herpes. 2.1.6 History of severe or acute ocular allergy within the last 3 months. 2.1.7 History of inflammatory corneal ulcer or uveitis within the last 12 months. 2.2 Systemic / non-ophthalmic exclusion criteria 2.2.1 Known hypersensitivity to one of the components of the investigational products. 2.2.2 History or active relevant systemic condition to be incompatible with the study to be likely to interfere with the study results or the patient safety according to investigator judgment. 2.3 Specific Exclusion Criteria for Women

2.3.1 Pregnancy or lactation

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 or condom) and is not surgically sterilised.

2.4 Exclusion Criteria Related to General Conditions

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 patient diary; way of life interfering with compliance).

2.4.3 Participation in this study at the same time as another clinical study.

2.4.4 Participation in this study during the exclusion period of another clinical study.

2.4.5 Patient previously included 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 investigation sites or of the sponsor's company.

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

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

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

<table>
<tr><td colspan="3">Before the screening visit</td><td>Screening
(D-14/D-10 à D1)</td><td>From Day 1
to Day 42</td></tr>
<tr><td>12 months</td><td>3 months</td><td>1 month</td><td>Run-in period</td><td>Treatment
period</td></tr>
<tr><td colspan="5">Cataract or ocular surgery</td></tr>
<tr><td></td><td colspan="4">Isotretinoïde, cyclosporine, tacrolimus, sirolimus, pimecrolimus
And others immune-suppressive medications
Topical corticoids and topical antihistaminics
Lachrymal plugs</td></tr>
</table>

	Any change in systemic medication Contact lenses Antihistaminic and steroid systemic medication Any ocular medication other than preservative free artificial tears (NaCl 0.9%) Any ocular medication including artificial tears

Table 1: Schedule of Visits and Procedures

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

3 SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION OF THE RESEARCH

3.1 Scientific Background and rationale of the research

3.1.1 Dry eye disease

Dry eye disease (DED) is defined as a multifactorial disease due either to insufficient tear production or excessive tear evaporation. Symptoms of discomfort and ocular damages are known to be related to tear hyperosmolarity and ocular surface inflammation (DEWS 2007b).

Dry eye can be caused by multiple aetiologies. Triggering factors include intrinsic and extrinsic elements such as age, gender, hormones, autoimmune disorders, local environment (in particular, low humidity and/or windy environmental conditions greatly contribute to ocular surface desiccation), use of video display, contact lens wear and exposure to medications/preservatives (e.g., benzalkonium chloride). Furthermore, dry eye sensations and symptoms were recently confirmed to be enhanced by seasonal conditions. These factors may lead to decreased tear production, or increased eye inflammation and tissue damage, and ultimately tear film breakdown, all of which can be associated with clinical symptoms (Pucker et al., 2016). Additionally, eye inflammation can inadvertently lead to further dysfunction of the eye's surface and its associated structures (e.g., lacrimal gland), in turn leading to further tear reduction and inflammation. Some aetiologies like the Sjögren's syndrome (SS) and conjunctival fibrotic diseases might result in severe ocular surface lesions.

The prevalence of DED is high and constantly increasing due to factors linked to life style (e.g., medications, especially the use of psychotropes, pollution, central heating, air-conditioned working environments, computer-based work, population ageing). Dry eye is currently estimated to affect between 5% and 35% of adults worldwide (Baudouin et al., 2017).

Eye dryness mostly gives rise to ocular symptoms. Common DED symptoms include pain, foreign body sensation, dryness or irritation, burning and light sensitivity. Visual deficiencies could be transitorily observed due to the alteration of tear optical qualities (Goto et al., 2002), or sometimes more prolonged due to induced corneal epitheliopathy (Baudouin, 2001). It is mostly harmless but can induce a functional disturbance for the patients. Forms altering the visual function are rare and

often related to co-morbidities such as trachoma, dermatitis, collagenosis, and exposure keratitis (Lemp, 1995).

Visual complaints are highly prevalent among dry eye patients. These are usually described as disturbed vision or blurry/foggy vision that clears temporarily with the blink. These transient changes can be profound, resulting in significant decrease of the contrast sensitivity and visual acuity, thus affecting workplace productivity and vision-related Quality of Life (QoL) (DEWS, 2007c).

The impact of dry eye on QoL is mediated through 1) pain and irritation symptoms, 2) effect on ocular and general health and well-being, 3) effect on perception of visual function, and 4) impact on visual performance. For example, the irritation symptoms of dry eye can be debilitating, resulting in both psychological and physical effects that impact QoL. Dry eye also limits common daily activities such as driving, and leads to contact lens intolerance (DEWS, 2007c).

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 (eye drops, fluid or more viscous substitute, or ophthalmic gels). In 2007, the Management and Therapy Subcommittee of the International Dry Eye Workshop confirmed the place of choice of artificial tear substitutes in the first line therapy for DED (DEWS, 2007a). According to the International Task Force Guidelines for Dry Eye, treatment recommendations are based on the disease severity, with a 4-level severity grading scheme based on ocular signs and symptoms (DEWS, 2007a). Eye drops of artificial tears are the treatment of choice for mild forms of dry eye. In cases of moderate involvement, artificial tears may be used as first line treatment but the rate of instillations is increased compared to mild forms, and combinations of different tear substitutes are commonly prescribed. In severe cases, artificial tears may be used in combination with other treatments (moist chamber goggles, inserts, continuous irrigation, and occlusion of the lachrymal points ...), and sometimes anti-inflammatory drugs (ciclosporin).
In addition to lubricating the eye, tears are also produced as a reflex response to various stimuli such as an injury or emotion. However, reflex tears do little to soothe a dry eye with watery eyes may still complain of irritation.

3.1.2 Rationale for the development of T2769

The requirements for artificial substitutes include a good ocular safety/tolerability and long residence time on the ocular surface (Schmidl et al., 2015). In addition, the deleterious effect of eye drop preservatives on the ocular surface is increasingly acknowledged, leading to the development of preservative-free formulations for the treatment of dry eye, as recommended by the Management and Therapy Subcommittee of the International Dry Eye Workshop (DEWS, 2007a).

A recent Cochrane review indicates a similar efficacy of most artificial tears, and that no agreement has been established about the best formulation for dry eye management (Pucker et al., 2016). In this context, the combination of several active agents with different mechanisms may be effective to further improve symptom relief and ocular comfort.

T2769 is a preservative-free combination of sodium hyaluronate 0.15% and trehalose 3%, associated with N-acetylaspartyl-glutamate (NAAGA) at 2.45%.

Both sodium hyaluronate 0.15% and trehalose 3% eye drops are currently marketed by Laboratoires THEA as preservative-free ophthalmic solutions effective and safe to moisten and lubricate the eye in case of dryness or sensation of fatigue (brand name: Hyabak® and Thealoz®, respectively) (Ramoth et al., 2013; Brjesky et al., 2014; Schmidl et al., 2015).

Importantly, a formulation combining sodium hyaluronate 0.15% and trehalose 3% is also marketed by Laboratoires THEA (brand name Thealoz® Duo or Théalose). The clinical experience with Thealoz Duo® largely demonstrated its efficacy in the management of DED (Pinto-Bonilla et al., 2015; Schmidl et al., 2015; Chiambaretta et al., 2017). In patients with moderate-to-severe DED, Thealoz Duo® was shown to be effective in reducing dry eye symptoms of stinging, itching, and blurred vision, with a better patient satisfaction compared to Vismed® eye drops (sodium hyaluronate only), particularly from the first month of treatment (Chiambaretta et al., 2017). Greater improvement of patient satisfaction was also found following treatment with Thealoz

Duo® in comparison to Systane® (Pinto-Bonilla et al., 2015). In addition, Thealoz Duo® was shown to be effective in improving the OSDI score, corneal and conjunctival staining, ocular signs such as chemosis, conjunctival hyperaemia, Schirmer test, TBUT (Pinto-Bonilla et al., 2015). A significantly higher increase of the tear film thickness was observed with Thealoz Duo® compared to Hyabak® eye drops in patients with moderate-to-severe DED (Schmidl et al., 2015). The same authors evidenced a considerably longer residence time of Thealoz Duo® at the ocular surface. This could be related to the interaction of trehalose with lipid membranes, which generates the surrounding hydration shell for the ocular surface (Schmidl et al., 2015). These studies thus highlight the clinical benefits of combining sodium hyaluronate and trehalose for the treatment of moderate-to-severe DED.

As regards NAAGA, the first ophthalmic solution containing this compound (Naaxia®) was registered in France in 1983 and made available on the French market in 1984 by Laboratoires THEA. Currently, NAAGA-based eye drops are marketed in 45 countries. A large number of clinical studies showed that NAAGA-based ophthalmic solutions are effective in improving ocular signs and symptoms in patients with conjunctivitis and blepharoconjunctivitis of allergic origin (Corre et al., 1991; Chanal et al., 1994; Gunduz et al., 1996; Denis et al., 1998; Leonardi et al., 2007; Lazreg et al., 2008). These medicinal products, which have been used for more than 20 years as anti-allergic agents, have a well-established use, with recognized efficacy and an acceptable level of safety. The efficacy of Naabak® eye drops (preservative-free NAAGA 4.9% eye drops) was also demonstrated in dry eye patients with a significant decrease in the expression of inflammatory markers, notably the antigen HLA-DR (Brignole-Baudouin et al., 2009). Importantly, this study confirmed the properties of NAAGA in the context of DED with a significant improvement of ocular symptoms (burning, foreign body sensation, itching, photophobia, heavy eyelid, sensation of wet eye, eye fatigue) and overall ocular comfort (Brignole-Baudouin et al., 2009).

Overall, the clinical experience with Thealoz Duo® highlighted the combined properties of sodium hyaluronate and trehalose (i.e., hydration and lubrication) in the management of DED. NAAGA also appears to present soothing properties, with an improvement of ocular symptoms and overall

comfort in DED patients. The ancillary effectiveness of NAAGA combined with Thealoz Duo® is expected to better soothe inflammation signs and symptoms.

Identification and description of the investigational productT2769 is a preservative-free, isotonic, colourless ophthalmic with a pH close to physiological values. It contains hyaluronic acid (0.15%), trehalose (3%) and NAAGA (2.45%) as main ingredients (see Table 4 for detailed composition of T2769). T2769 is packed in a multidose white polyethylene ABAK® system bottle allowing a 3-months shelf life after first opening.

In the absence of any preservatives in the solution, anti-microbial protection of the solution is ensured by a membrane filter with very low porosity (0.2 µm).

T2769 is intended to protect, hydrate, lubricate and soothe the eye in case of moderate-to-severe dry eye syndrome or sensation of fatigue (Instructions for use of T2769, v0.1 01-06-2017). T2769 is indicated for patients suffering from stinging, burning, itching or irritation of the eyes. These symptoms can be caused by environmental factors such as wind, smoke, pollution, dust, sunny or cold conditions, dry heat, air conditioning, plane journeys, and long hours working in front of a computer screen.

3.2 Justification of the study design regarding to the investigational products

Due to the different causes of dry eye, patients are not always satisfied with their current lubricants, the combination of different agents with different modes of action may be effective to reduce DES symptoms and signs. Moreover, unfixed combinations require a higher number of administrations and are not convenient for the patient's everyday life. On the contrary, a fixed combination allows a lower number of administrations, and thereby may provide better compliance for patients requiring combination of at least two lubricants.

The bibliographical review resulted in confirming the efficacy and safety of hyaluronic acid 0.15% and trehalose 3% (individually or combined in Thealoz Duo®), as well as NAAGA 4.9%, in the

management of DED. The purpose of the T2769 project is to develop a new preservative-free formulation combining these three compounds (NAAGA at 2.45%) for the treatment of moderate-to-severe DED. The ancillary effectiveness of NAAGA combined with Thealoz Duo® is expected to better soothe inflammation signs and symptoms.

This non-comparative, open-label study is a pilot study designed for the preliminary assessment of the efficacy and safety of T2769, administered 3 to 6 times daily (in each eye) for 6 weeks (42 days) in patients suffering from moderate-to-severe DED. The primary and secondary endpoints of this clinical study (ocular VAS, Oxford grading scheme, Van Bijsterveld score, ocular signs and symptoms, ocular tolerance…) have been taken into consideration based on the clinical literature review (DEWS 2007a; Brignole-Baudouin et al., 2009; Pinto-Bonilla et al., 2015; Chiambaretta et al., 2017). Consequently, these endpoints are clinically relevant, clearly defined and assessed at specified time points in order to provide clinical evidence on the efficacy and tolerance of T2769 in its intended use (*i.e.*, improvement of the ocular signs and symptoms in DED patients).

3.3 Description of the Studied Population

The objective of this study is to evaluate the efficacy and safety of the investigational product in patients with moderate-to-severe dry eye syndrome. For this purpose, patients (men and women) presenting a known dry eye syndrome requiring artificial tears within the last 3 months will be included among the patients of the different centers. The dry eye syndrome will be checked at the inclusion visit based on different tests and scores (Oxford scale, Schirmer test, Tear Break-Up Time, conjunctival hyperemia) and the ocular symptoms felt by the patient (itching/pruritus, burning/irritation, light sensitivity).

3.4 Summary of potential benefits and risks for the patients

The literature analysis points out the clinical benefits of the three main ingredients of T2769 in the treatment of DED. Clinical studies on sodium hyaluronate 0.15% (Hyabak®), trehalose 3% (Thealoz®) and the combination of sodium hyaluronate 0.15% and trehalose 3% (Thealoz Duo®) confirmed that these agents are valuable options in the management of DED (i.e., allowing

protection, hydratation and lubrication of the eye, and improving ocular symptoms and signs) (Ramoth et al., 2013; Brjesky et al., 2014; Schmidl et al., 2015; Pinto-Bonilla et al., 2015; Chiambaretta et al., 2017). The treatment of dry eye patients with NAAGA 4.9% was also shown to significantly decrease the expression of inflammation markers and to improve ocular symptoms and overall comfort (Brignole-Baudouin et al., 2009).

As regards safety, the combination of sodium hyaluronate 0.15% and trehalose 3% (Thealoz Duo®) is well tolerated and safe for the treatment of DED. In a recent clinical study conducted in DED patients (Chiambaretta et al., 2017), the incidence of ocular AEs was lower for Thealoz Duo® (1 patient, 1.9%) than for the reference product Vismed® (sodium hyaluronate 0.18% eye drops) (7 patients, 13.2%). The ocular AE (moderate viral conjunctivitis) experienced by the patient in the Thealoz Duo® group was not considered to be treatment-related by the investigator. No serious adverse event was reported in this study. For NAAGA (at 4.9%), among the 53 dry eye patients included in the Brignol-Baudouin's study (Brignole-Baudouin et al., 2009), one patient reported worsening of an existing blepharitis (for which the relation to treatment was considered doubtful by the investigator) and another patient reported hyperaemia, burning sensation and lid swelling (considered as possibly related to treatment) in the Naabak® group. No serious adverse event was reported in this study.

Currently, the product information mentions the following side effects for Thealoz Duo® and Naabak® (NAAGA at 4.9%), respectively:

- *"You may have mild eye irritation, although is very unusual"* (Thealoz Duo® IFU, 2015)
- "*Possibility of brief sensation of burning or stinging at instillation*" (Naabak SmPC, 2016)

Overall, the expected benefits for the patients are improvements of ocular signs and symptoms related to dry eye syndrome, while the expected risks upon use of T2769 are mild eye irritation (considered to be very unusual) or brief sensations of burning or stinging upon instillation. Thus, based on the efficacy and safety data available, the Sponsor considers that the benefit/risk ratio of T2769 is favourable for use in clinical trials. T2769 eye drops could be regarded as a new option in the treatment of moderate-to-severe DED.

3.5 Conformity declaration to GCP and applicable regulatory requirements

The research will be performed on patients, in accordance with GCP (Good clinical practice ICH E6 R2-EMA/CHMP/ICH/135/1995), with the Tunisian regulations and especially decree n° 90-1401 of 3 September 1990, setting the conditions of medical or scientific experimentation of medicinal products intended for human medicine, and with Helsinki declaration and its updates.
After having received a complete information on the investigational product and the study realization's conditions, each subject will confirm his consent, in writing, on a specific form in double exemplars: the original one for the investigator, the second one for the subject.
This protocol has been submitted to Ethics Committee and Competent Authority for approval.

The material and the investigational product given for the test will be used only under the conditions stipulated by the protocol.
Any modification to the protocol will be treated as a substantial or non-substantial modification, according to its nature, and will be submitted for opinion/approval to the Ethic Committee and/or Competent Authority.
Any violation to this protocol may result in the early termination of the research center.

4 OBJECTIVE(S) OF THE RESEARCH

4.1 Main objective

To assess the efficacy T2769 in patients with moderate to severe Dry Eye Syndrome.

4.2 Secondary objective(s)

To assess the safety of T2769

5 RESEARCH PLAN AND DESIGN

5.1 Description of the evaluation criteria

5.1.1 Main Assessment Criterion

- Evolution of the ocular symptomatology on a Visual Analog Scale (VAS) between D1 and after 42 days of treatment (D42).

5.1.2 Secondary Assessment Criteria

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

5.1.3 Other evaluation parameters

5.1.3.1 Other evaluation parameters at D14

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

5.1.3.2 Other assessment parameters at D14 and D42

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

5.1.3.3 Safety criteria

After 14 days and 42 days of treatment with the T2769:

- Ocular symptoms upon instillation: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation and other symptoms will be graded by the patient.

After 42 days of treatment with the T2769

- Far best corrected visual acuity assessment.
- Ocular tolerance assessment by the investigator
- Ocular tolerance assessment by the patient.

During the 42 days of treatment with T2769:

Ocular and systemic adverse events (AE).).

5.2 Methodology of the research

5.2.1 Study design

The study will be:

- ♦ in open,
- ♦ non-comparative,
- ♦ single dose,
- ♦ multicentre
- ♦ on ambulatory patients,

Study Flow Chart

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

5.3 Description of the methods used to minimize or avoid biases

Not applicable, open study.

5.4 Conditions of study participation for patients

5.4.1 Duration of the study

Foreseen beginning of the study: September 2017

Foreseen end of the study: May 2018

Global duration of the study: 9 months

Global duration by subject: approximately 2 months

5.4.2 Study schedule

Screening visit (D-14 to D -10) – Visit# 1

- The ophthalmologist will propose to his/her patient to participate in the clinical study.
- Information of the patient about the aim and study proceedings.
- Signature of information sheet and consent form in two copies by the patient and the investigator.
- Questioning about ocular medical and surgical history,
- Questioning about previous and concomitant ocular and non-ocular treatments,
- History of Dry Eye
- Symptomatology within the last 48h on a VAS,
- Questioning about ocular symptoms,
– Measurement of the far best corrected visual acuity in both eyes.
- Measurement of conjunctival hyperaemia with MacMonnies photographic scale,
- Slit lamp examination with fluorescein and lissamine green colorations for measuring:
    - Tear Break Up Time (TBUT),
    - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal coloration by lissamine),
    - Van Bijsterveld score (Lissamine green coloration).
- Checking of inclusion and exclusion criteria.

- If the patient is eligible, distribution of preservative free artificial tears (Physiol®) to be used 3 to 6 times per day in both eyes until the inclusion visit.

Inclusion visit (D1) - Visit# 2

- The patient will bring back the Physiol®.
- Questioning about Physiol® compliance.
- Collection of adverse events and concomitant treatments.
- Symptomatology within the last 48h on a VAS,
- Questioning about ocular symptoms,
- Measurement of OSDI score.
- Measurement of conjunctival hyperaemia with MacMonnies photographic scale,
- Schirmer test (without anesthesia).
- Slit lamp examination with fluorescein and lissamine green colorations for measuring:
    - Tear Break Up Time (TBUT),
    - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal coloration by lissamine),
    - Van Bijsterveld score (Lissamine green coloration).
- Checking of inclusion and exclusion criteria.
- If the patient is eligible, inclusion of the patient.
- The ophthalmologist will distribute the investigational product for the period D1-D14 and explain the mode of use of the treatment.

D14 ± 1 day - Visit# 3

- The patient will bring back the treatments (used and non-used).
- Questioning about dose regimen compliance
- Collection of adverse events and concomitant treatments.
- Symptomatology within the last 48h on a VAS,
- Questioning about ocular symptoms,
- Questioning about ocular symptoms upon instillation,
- Questioning about soothing sensation.
- Measurement of OSDI score.
- Measurement of conjunctival hyperaemia with MacMonnies photographic scale,

- Schirmer test (without anesthesia).
- Slit lamp examination with fluorescein and lissamine green colorations for measuring:
    - Tear Break Up Time (TBUT),
    - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal coloration by lissamine),
    - Van Bijsterveld score (Lissamine green coloration).
- The ophthalmologist will distribute the investigational product for the period D14-D42.
- Ocular efficacy assessment by the investigator.
- Ocular tolerance assessment by the investigator and the patient.

D42 ± 5 days - Visit# 4

- The patient will bring back the investigational products (used and non-used).
- Questioning about dose regimen compliance
- Collection of adverse events and concomitant treatments.
- Symptomatology within the last 48h on a VAS,
- Questioning about ocular symptoms,
- Questioning about ocular symptoms upon instillation,
- Questioning about soothing sensation.
– Measurement of the far best corrected visual acuity in both eyes.
- Measurement of OSDI score.
- Measurement of conjunctival hyperaemia with MacMonnies photographic scale,
- Schirmer test (without anesthesia).
- Slit lamp examination with fluorescein and lissamine green colorations for measuring:
    - Tear Break Up Time (TBUT),
    - Oxford 0-15 grading scheme (corneal coloration by fluorescein, temporal and nasal coloration by lissamine),
    - Van Bijsterveld score (Lissamine green coloration).
- Ocular efficacy assessment by the investigator.
- Ocular tolerance assessment by the investigator and the patient.

6 STUDIED POPULATION

6.1 Inclusion criteria

Criteria at the screening visit

1.1. Informed consent signed and dated.

1.2. Man or Woman aged ≥ 18 years.

1.3. Known Dry Eye Syndrome requiring artificial tears within the last 3 months prior to study screening.

Criteria at the inclusion visit

1.4. Patient having used only preservative free artificial tears (Physiol®) as ocular medication during the run-in period (from D-14/D-10 to D1).

1.5. No ocular instillation at least 2 hours prior to the inclusion visit.

1.6. Patient having at least one *Eligible Eye*, defined by both following conditions:

- Global 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

1.7. Conjunctival hyperaemia: Score ≥ 1 and ≤ 3 (Mc Monnies scale)

1.8. At least one ocular symptom: itching/pruritus; burning/irritation; light sensitivity with a severity score ≥ 1 and ≤ 3 for each symptom,

1.9. Diagnosis of moderate to severe dry eye syndrome defined by OSDI Score ≥ 18.

6.2 Exclusion criteria

2.1. Ophthalmic Exclusion Criteria in at least one eye

2.1.1. Best far corrected visual acuity ≤ 2/10

2.1.2. Severe blepharitis

2.1.3. Severe Dry Eye associated to:

- ✓ Ocular Rosacea
- ✓ Progressive Pterygium
- ✓ Eyelid malposition
- ✓ Corneal dystrophy
- ✓ Ocular neoplasia
- ✓ Filamentous keratitis
- ✓ Corneal neovascularisation
- ✓ Orbital radiotherapy

2.1.4. History of severe ocular traumatism, ocular infection or ocular inflammation within the last 6 months.

2.1.5. History of ocular herpes.

2.1.6. History of severe or acute ocular allergy within the last 3 months.

2.1.7. History of inflammatory corneal ulcer or uveitis within the last 12 months.

2.2. Systemic / non-ophthalmic exclusion criteria

2.2.1. Known hypersensitivity to one of the components of the investigational products.

2.2.2. History or active relevant systemic condition to be incompatible with the study to be likely to interfere with the study results or the patient safety according to investigator judgment.

2.3. Specific Exclusion Criteria for Women

2.3.1. Pregnancy or lactation

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 or condom) and is not surgically sterilised.

2.4. Exclusion Criteria Related to General Conditions

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 patient diary; way of life interfering with compliance).

2.4.3. Participation in this study at the same time as another clinical study.

2.4.4. Participation in this study during the exclusion period of another clinical study.

2.4.5. Patient previously included 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 investigation sites or of the sponsor's company.

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

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

The prohibited treatments (or prohibited modifications of treatment regimen) and their periods of use prohibition are listed in the following table 2

<table>
<tr><td colspan="3">Before the screening visit</td><td>Screening
(D-14/D-10 à D1)</td><td>From Day 1
to Day 42</td></tr>
<tr><td>12 months</td><td>3 months</td><td>1 month</td><td>Run-in period</td><td>Treatment period</td></tr>
<tr><td colspan="5">Cataract or ocular surgery</td></tr>
<tr><td rowspan="6"></td><td colspan="4">Isotretinoïde, cyclosporine, tacrolimus, sirolimus, pimecrolimus
And others immune-suppressive medications
Topical corticoids and topical antihistaminics
Lachrymal plugs</td></tr>
<tr><td colspan="3"></td><td colspan="2">Any change in systemic medication</td></tr>
<tr><td colspan="3"></td><td colspan="2">Contact lenses</td></tr>
<tr><td colspan="3"></td><td colspan="2">Antihistaminic and steroid systemic medication</td></tr>
<tr><td colspan="3"></td><td>Any ocular medication other than preservative free artificial tears (NaCl 0.9%)</td><td></td></tr>
<tr><td colspan="4"></td><td>Any ocular medication including artificial tears</td></tr>
</table>

6.3 Restrictions and Prohibitions

- Patients must not take part in any other clinical study whilst taking part in this study.
- Patients must not use other ocular medication than the products given during the study (Physiol® from Screening visit to D1 and T2769 from D1 to D42).
- No ocular instillation at least 2 hours prior to the inclusion visit

6.4 Sample size

The primary efficacy criterion is the change from baseline in ocular symptoms at Day 42 assessed using a Visual Analogue Scale. Assuming that the mean change is 12, the standard deviation is 23, the correlation between pairs is 0.4, a total of 50 evaluable patients achieves a power of at least 90% (calculated power = 91%) for the two-sided test for no difference with a normal distribution and a significance level of 5% (Table 3).

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

Table 3. The POWER procedure: paired t test for mean difference.

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

Fixed Scenario Elements
Computed Power
Power
0.910

6.5 Recruitment procedure

Patients will be recruited among the patients of the different centers.

6.6 Study End

6.6.1 Definition of the study end

The study end is defined as the Last Subject Last Visit.

6.6.2 Early Study discontinuation

6.6.2.1 Criteria and modalities of premature end of treatment or subject exclusion from the study

The patient may voluntarily withdraw from the study at any time without penalty and for any reason without prejudice to her future medical care (Declaration of Helsinki).

The patient must be withdrawn from the study if, in the opinion of the investigator, there is any situation or condition which puts the patient at significant risk.
The investigator may decide to withdraw a patient for the following reasons:

- Adverse event(s) or Adverse Effect(s) necessitating study discontinuation ,
- Ocular dryness worsening from baseline according to the investigator's judgement and/or ocular examination

- Lack of efficacy: if the patient or the investigator does not feel that the treatment has adequately relieved his/her symptoms,
- Patient's request.
- Other reason.

In case of withdrawal from the study, the investigator will prescribe the best appropriate treatment to the patient.

In all cases, the date and the primary reason for withdrawal, must be recorded on the case report form (CRF) and patient files (source documentation).

If a patient is prematurely withdrawn from the study for any reason, the investigator must make every effort to perform the evaluations described for the Day 42 visit.

The patient discontinued for AE(s) will be followed-up after discontinuation until the event is resolved or considered medically stable by the investigator.
If a patient is lost-to-follow-up, the investigator must do his/her best to contact the patient initially by phone, then by letter, and finally by certified mail. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or her general physician. The evidence of these contacts must be recorded in the patient files.

6.6.2.2 Modalities for patients' replacement

Drop-outs will not be replaced as it is foreseen to include 55 patients on D1 to expect at least 50 patients to be analysed.

6.6.2.3 Modalities for patients follow-up

When the premature exit is due to an adverse effect, the subject will be followed until the resolution or the stabilization of the symptoms.

6.7 Modalities for obtaining informed consent of the patients participating in the research

Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient. The patient must be given the opportunity to ask questions, and have reasonable time for reflection before giving herconsent.

Written informed consent must be obtained prior to initiation of any study procedures or any discontinuation of current medication. No measures whatsoever described in the protocol shall be undertaken without such consent indicating that the patient has been given both verbal and written information about the study and the investigational product.

The informed consent form shall be signed and dated by the patient and the investigator. Two original consent forms will be signed and one shall be included in the investigator's study file, the other one shall be given to the patient. No copy will be given to the Sponsor.

7 INVESTIGATIONAL PRODUCT(S)

7.1 Description of investigational product

T2769 is an isotonic, neutral, clear colourless solution with a pH close to physiological values. Sodium Hyaluronate and Trehalose are the main ingredients and complete formula is detailed in Table 4.

*** *A diluted solution of NaOH is used to adjust pH around 7.2*

7.2 Dosage

Dose regimen for 42 days: one drop in each eye, 3 to 6 times daily

7.3 Modalities of use

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.

7.3.1 Route and mode of administration

Ocular route.

7.3.2 Packaging

T2769 is packed in a multidose white polyethylene ABAK® system bottle (10 mL) allowing a 3-months shelf life after first opening. 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 in several currently marketed eye drops.

Each investigational product*, i.e.* complete treatment for one patient, will contain 5 vials of T2769 distributed among 2 treatment periods D1-D14 and D14-D42.

Each treatment unit, *i.e.* complete treatment for one patient, will be packaged as follows:

Packaging	D1-D14	D14-D42
Primary	2 vials	3 vials
Secondary	1 cardboard carton	1 cardboard carton
Final	1 cardboard carton	

7.3.3 Labelling

The content of the labelling will be in accordance with the Good Manufacturing Practices and the local specifications and requirements.

The cardboard cartons for period D1-D14 and for period D14-D42 will carry detachable labels (flag label) bearing the protocol number, treatment number and the treatment period (D1-D14) or (D14-D42). These labels will be torn off by the person dispensing the medication to the patient, and will be stuck in the space provided in the CRF in order to record the dispensing procedure.

7.3.4 Preservation and Storage

The investigational products will be provided by the sponsor to the study site pharmacist. An acknowledgment of receipt will be completed by the pharmacist and returned to the sponsor.
The investigational products will be stored under the supervision of a pharmacist approved for the study under suitable safety conditions ensuring proper storage, at room temperature (below 25°C) in a dedicated air-conditioned room. This room is locked and access controlled.
The investigational products will be only used following the specifications detailed in this protocol, and only for patients having been randomized by the investigator.

7.3.5 Dispensing and accountancy of investigational products supplies

The investigational product should only be dispensed only under the supervision of a physician approved for the study. The investigator (or delegate) is responsible for dispensing the investigational products to the patients who are included in the study. The investigational products must not be administered to patients who are not included in the study.

A specific accountancy form provided by the Sponsor must be kept current and must identify the subject number/the number of the product dispensed, and the amount of product dispensed to and returned by each subject at each visit, with the corresponding dates.
All products supplies (empty containers, as well as partly used and unused products must be available for inspection at every monitoring visit. The CRA or sponsor delegate should verify the investigational site's products accountability records against record of administrated doses in the CRF.
All products (wasted and unused) must be returned by the patients to the investigator at each visit and by the investigator to the sponsor at the end of the study.

Compliance with the investigational product will be checked at each visit by the investigator and reported on the Study Drug Form. In order to verify investigational product compliance, patients will be questioned during the protocol visits about their compliance. In addition, the patients will also have to report information about his compliance on a diary during the treatment period. This diary will not be recorded onto database.

7.4 Product allocation – Randomization - Blinding

Not applicable. All patients will receive the same product.

7.5 Treatment(s) and associated product(s)

Cf 7.5.4

7.5.1 Authorized medication(s) and treatment(s)

Any concomitant medication at inclusion of the subject into the study must be reported on the source document and in the study CRF at the initial visit and will be taken into consideration by the Investigator deeming study eligibility.
Any modification on these medications during the study *must* be reported on the source document and in the study CRF.
Use of any concomitant medication will be recorded in the CRF with the following information:

- Indication for use of the treatment;
- Name of the drug, type of formulation, and unit strength;

- Dose administered;
- Duration of treatment (start and stop date).

7.5.2 Non-authorized medication(s) and treatment(s)

The treatments specified in paragraph 6.2. are not authorized during all the duration of whole study period. More generally, patients will not be allowed to take any medication which might interfere with the efficacy or interpretation of the study end point evaluations specified in this protocol, unless the subject elects to withdraw from the study. If there is any question whether a particular concomitant medication is allowed, the Investigator should consult the Sponsor.

7.5.3 Rescue treatment

If case of adverse reaction affecting subject well-being, the investigator is authorized to interrupt the use of the investigational product and prescribe to the subject a rescue treatment/medication.
The adverse medical event will be recorded in the subject's CRF, including details on rescue medication, and will be managed according to section 7.5.1.

7.5.4 Auxiliary product used but not studied

During the run-in period, from screening visit to D1, Physiol® will be given to the patients (artificial tears without preservative).

Name: Physiol®
Composition: NaCl 0.9%
Form: sterile solution
Administration route: ocular route
AMM: 9093032H
Date AMM: 13/10/1993
Dosage: one drop in each eye 3 to 6 times daily

8 EFFICACY ASSESSMENT

8.1 Description of efficacy assessment parameters

8.1.1 Primary efficacy variable

The primary efficacy variable will be the symptomatology within the last 48 hours on a VAS

Symptomatology evaluation (global evaluation for both eyes) will be assessed by the patient at each visit according to the following:

"Please mark a vertical line on the horizontal line, indicating your level of ocular discomfort due to ocular dryness within the last 48 hours". VAS will be a 100 mm line: 0 mm = No discomfort, 100 mm = Maximal discomfort.

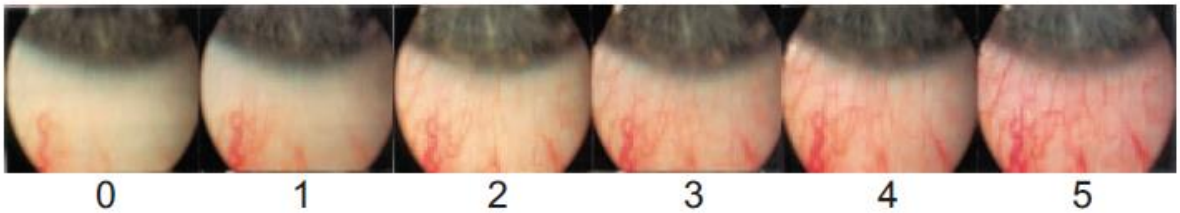
0	100
No discomfort	Maximal discomfort.

8.1.2 Other efficacy variables

8.1.2.1 Conjunctival hyperaemia using Mac Monnies photographic scale

The conjunctival hyperaemia will be assessed using the Mac Monnies photographic scale (Figure 1). This test will be performed at each visit.

Figure 1 – Mac Monnies photographic scale



This test will be performed in both eyes at each visit. The value at D1 will be the baseline value.

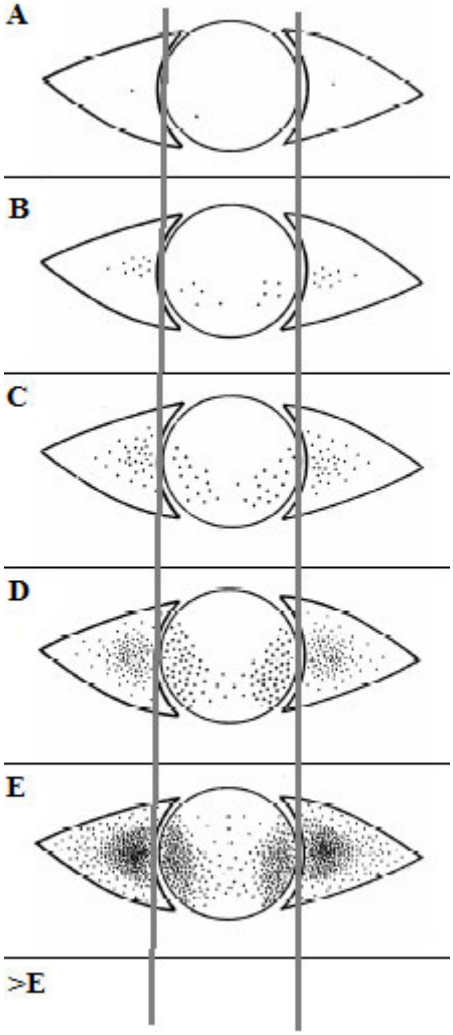
8.1.2.2 Global ocular staining (Oxford scale)

Cornea and conjunctiva staining will be assessed with a slit lamp after instillation of unpreserved fluorescein in the examined eye. In order to optimize the fluorescein staining signal without any masking by the fluorescence quenching effect, 1 drop of fluorescein will be instilled in the examined eye.

Cornea and conjunctiva staining is represented by punctate dots on a serie of panels (A-E). Staining ranges form 0-5 for each zone and from 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on the log scale (Oxford scale) below (Figure 2):

The Oxford score will be measured at each visit in both eyes. The value at D1 will be the baseline value.

Figure 2 – Oxford 0-15 grading scheme

<table>
<tr><th colspan="7">OXFORD SCHEME (15 POINTS)</th></tr>
<tr><th colspan="3">Panel
RE</th><th>Grade</th><th>Criteria</th><th colspan="2">Panel
LE</th></tr>
<tr><td colspan="3"> 
</td><td>0

I

II

III

IV

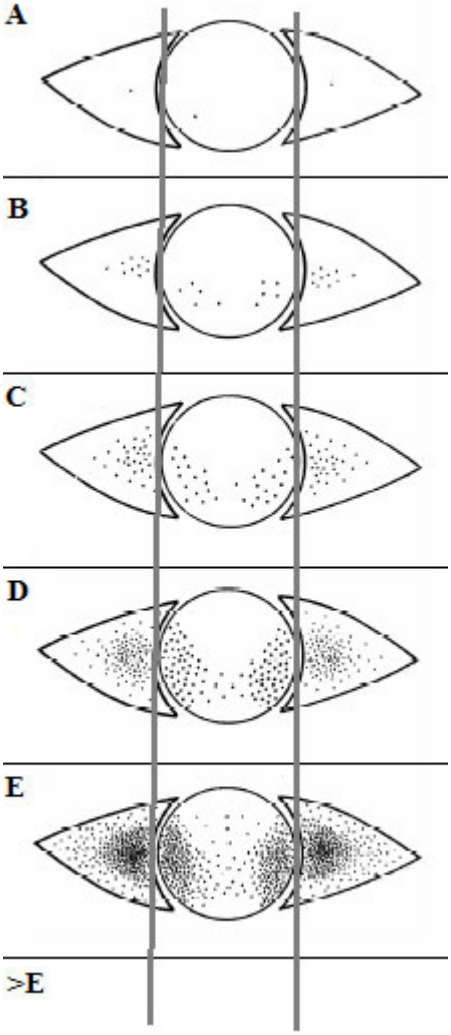
V</td><td>Equal to or less than panel A

Equal to or less than panel B, greater than A

Equal to or less than panel C, greater than B

Equal to or less than panel D, greater than C

Equal to or less than panel E, greater than D

Greater than E</td><td colspan="2"> 
</td></tr>
<tr><td>Temporal bulbar conjunctiva</td><td>Corneal area</td><td>Nasal bulbar conjunctiva</td><td colspan="2" rowspan="3">USE GRADE 0 TO 5 FOR EACH AREA</td><td>Nasal bulbar conjunctiva</td><td>Corneal area</td><td>Temporal bulbar conjunctiva</td></tr>
<tr><td>|___|</td><td>|___|</td><td>|___|</td><td>|___|</td><td>|___|</td><td>|___|</td></tr>
<tr><td colspan="3">TOTAL GRADE : |___|___|</td><td colspan="3">TOTAL GRADE : |___|___|</td></tr>
</table>

8.1.2.3 Van Bijsterveld score

The global ocular staining will also be assessed by the Van Bijsterveld score from the lissamine green coloration.

This test will be performed in both eyes at each visit. The value at D1 will be the baseline value.

Impregnated paper 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 3). The corneo-conjunctival exposed surface is separated in 3 parts: nasal bulbar conjunctive, corneal area, and temporal bulbar conjunctive. The following score will be attributed to each of these parts with the help of a visual figure representing each degree of staining:

(0) = No coloration.

(1) = Some punctuations.

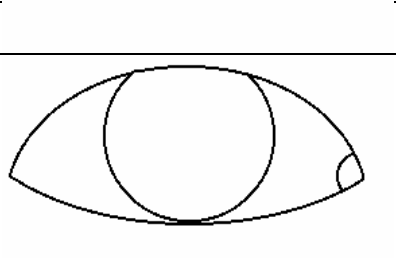
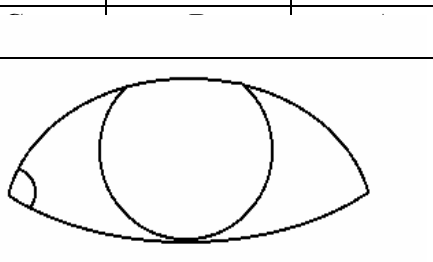
(2) = Well defined punctuations.

(3) = Total coloration.

The total score is the addition of the scores obtained in the 3 parts (nasal, corneal and temporal).

Figure 3 – 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**
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.

8.1.2.4 Ocular Surface Disease Index (OSDI)

The impact of the disease on the patient's daily activities will be assessed by the Ocular Surface Disease Index described in Figure 4. It will be measured on D1, D14 and D42

Figure 4 – Ocular Surface Disease Index

Have you experienced any of the following during the last week?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor 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?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	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?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A

11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	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)

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

8.1.2.5 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 and temporally downwards. 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 both eyes at each visit. The value at D1 will be the baseline value.

8.1.2.6 Tear Break-Up Time (TBUT)

The TBUT will be done at each visit. The value at D1 will be the baseline value.
The tear break-up time will be measured 3 times rapidly after the instillation of one drop of fluorescein. The TBUT value analyzed will be the sum of the 3 measurements.
This test will be performed in both eyes at each visit. The value at D1 will be the baseline value.

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?"

The severity of the following ocular symptoms will be assessed at each visit: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation, light sensitivity as follows:

0 = Absent (absent)

1 = Mild, present but not disturbing (présent mais non gênant)

2 = Moderate, disturbing, but not limiting with daily activities (gênant, mais ne limitant pas les activités quotidiennes)

3 = Severe, very distressing and interfering with daily activities (très gênant et limitant les activités quotidiennes)

The ocular symptoms will be assessed in global for both eyes at each visit. The value at D1 will be the baseline value.

8.1.2.8 Soothing sensation

The soothing sensation felt by the patient within 15 min after IP instillation after 14 and 42 days of treatment will be assessed according to the following scale:

(0) = None,

(1) = Mild,

(2) = Moderate,

(3) = Important

The soothing sensation will be assessed in global for both eyes at each visit post-baseline.

8.1.2.9 Ocular efficacy assessment by the investigator

The evaluation of the overall efficacy of investigational product will be assessed by the patient and by the investigator on D14 and D42, in global for both eyes, using the following rating scale:

(3) = Very satisfactory,

(2) = Satisfactory,

(1) = Not very satisfactory,

(0) = Unsatisfactory.

8.2 Methods and calendar for measuring, collecting and analysing efficacy assessment parameters

Study procedures	D1 (Baseline)	Day 14 (+/- 1 day)	Day 42 (+/- 5 days)
OSDI score	X	X	X
Conjunctival hyperaemia	X	X	X
Schirmer test	X	X	X
TBUT	X	X	X
Oxford 0-15 score	X	X	X
Van Bijsterveld score	X	X	X
Symptomatology evaluation (VAS)	X	X	X
Ocular symptoms	X	X	X
Soothing sensation		X	X
Ocular efficacy assessment by the investigator		X	X

9 ASSESSMENT OF SAFETY

9.1 Description of the safety assessment parameters

9.1.1 Adverse events

Ocular and systemic AEs will be reported at each contact with the patient (visits on D1, D14 and D42).
The handling of adverse events is detailed in section 9.3.

9.1.2 Far best-corrected visual acuity in both eye

Far Best-corrected visual acuity will be measured at the screening visit (visit #1) and on Day 42 visits with the patient's best correction using a Snellen chart.
The value at screening visit will be the baseline value.

9.1.3 Ocular tolerance assessment by the patient and the investigator

The ocular tolerance of the investigational product will be assessed on D14 and D42 by the patient and the investigator, in global for both eyes, using the following rating scale:

(3) = Very satisfactory,
(2) = Satisfactory,
(1) = Not very satisfactory,
(0) = Unsatisfactory.

9.1.4 Ocular symptoms upon instillation

Ask the patient:

"Have you felt any ocular discomfort/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.

burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, and other symptoms will be graded by the patient.

according to the following severity scale and with their duration:

(0) = Absent.

(1) = Mild: present but not disturbing.

(2) = Moderate: disturbing, but not limiting with daily activities.

(3) = Severe: Very distressing and interfering with daily activities.

The ocular symptoms upon instillation will be assessed in global for both eyes at each visit post-baseline.

9.2 Foreseen schedule for measuring, collecting and analysing these parameter

Study procedures	Screening visit (D-14/D-10)	D1	Day 14 (± 1 day)	Day 42 (± 5 days)
Ocular symptoms upon instillation			X	X
Far Best Corrected Visual Acuity (FBCVA) in both eyes	X			X
Adverse events		X	X	X
Ocular tolerance assessment by the investigator			X	X
Ocular tolerance assessment by the patient			X	X

9.3 Procedures for collection, registration and notification of adverse events

9.3.1 Definitions

9.3.1.1 Definition of adverse event (AE)

Adverse Event (AE): any untoward medical events that occurs in a patient who has accepted the participation in the study and which does not necessarily have a causal relationship with the Investigational Product (IP).

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the product.

An AE may include, but is not limited to:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the IP (Test product or comparator product)
- An effect of an auxiliary product
- Event unrelated to participation in the clinical study
- A combination of one or more of these factors

Adverse Drug Reaction (ADR): untoward and unintended response in a patient to the IP which is related to any dose administered to that patient.

Unexpected ADR: An adverse reaction is unexpected when the nature and severity is not consistent with the information about the medicinal product set out in the investigator's brochure relating to the trial in question.

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 CRF.

9.3.1.2 Definition of a Serious Adverse Event (SAE) or Reaction

Regarding the clinical study design and the regulatory requirements, A **serious Adverse event** is:

Any untoward medical occurrence or effect that at any dose 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 *(**pregnancy**, accidental or voluntary overdose, cancer or any other unfavourable medical event which is not fatal, life-threatening, and does not require hospitalisation, but requires urgent and intensive treatment*).

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

9.3.1.3 Definition of a new event

New events related to the conduct of a trial or the development of an IMP likely to affect the safety of patients, such as: — a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial, — a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease, — a major safety finding from a newly completed animal study (such as carcinogenicity), — a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor.

9.3.1.4 Definition of the severity of an Adverse Event/Reaction

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 6.6.8.4 "Reporting Serious Adverse Events" for having the definition of an SAE).

9.3.1.5 Relationship with the tested product

The investigator will assess the causality/relationship between the IP 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 tested product and cannot be reasonably explained by other factors (*e.g: concomitant therapy, patient condition, and/or other intervention*).

2 NOT RELATED A simultaneous disease, a simultaneous treatment or any other known condition clearly triggers the adverse

9.3.2 Documentation and notification

9.3.2.1 Documentation and reporting of Adverse Events / Reactions

The principal investigator shall:

a) record in the CRF every **adverse event** and adverse reaction, together with an assessment,

b) adverse event reporting will extend from signing of informed consent until the final study visit.

c) report to the sponsor, without unjustified delay, all serious adverse events and reactions; this information shall be promptly followed by detailed written reports,

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

All AEs, regardless of the relationship to the investigational product, will be recorded in the CRF.

All AE reports should contain: **a brief description of the event, localization, date and time of onset, duration (hours or days), intensity of symptoms (severity), treatment required, relationship with IP and protocol procedure, action taken with the IP, outcome, date and time of resolution and whether the event is classified as serious.**

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the investigator and Medical expert, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

9.3.2.2 Documentation and reporting of Serious Adverse Event by the investigator to the sponsor

In case of Serious Adverse Event, the Investigator must:

1. Complete the relevant CRF pages and the SAE form with all available initial information

   Immediately scan and send out the completed SAE form to the

   trialsafety@laboratoires-thea fr whilst copying the field CRA of the CRO.

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

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

   GlobalSafety and MedInfo Department

   Laboratoires théa

   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 IP. 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 CRF:

- Demography
- Medical and surgical history
- Previous and concomitant medication
- Study medication administration record

The Investigator is responsible for ensuring the follow-up of any patient who experiences an SAE during the study. 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 study documents, the Investigator will retain a copy of the SAE form for 15 years.

Any SAE occurring **within 1 month after the end of the study** and considered to be related to the IP, and therefore deemed as a possible Serious Adverse Drug reaction , must be reported to the Sponsor

After consultation with Laboratoires THÉA, the Investigator may be required to provide information about certain SAE to the independent ethics committee (IEC) according to the institutional policy.

9.3.2.3 Notification of the SUSAR by the sponsor to the NCA

All suspected adverse reaction related to an investigational product which occur in the concerned trial, and that are both unexpected and serious (SUSARs) must be reported to the Competent Authorities and Independent Ethics Committee:

- as soon as possible but not later than 7 calendar days in case of fatal or life threatening SUSARs,
- as soon as possible but not later than 15 calendar days for all other SUSARs.

The Sponsor must declare to the Competent Authorities and Independent Ethics Committee, with a follow-up report, any complementary relevant information concerning unexpected serious adverse effects. In case of fatal or life threatening SUSARs, this complementary information is notified in a new delay of 8 days from the delay of 7 days mentioned above, and a new delay of 15 days for all others SUSARs .

9.3.2.4 Sponsor's annual report to the Competent Authority and to the Ethics Committee

Once per year for the duration of the research or on request the sponsor transmits a safety report with all the available safety information to the CA and the EC. This report includes notably, the list of all the suspected serious adverse reactions and an analysis of the information regarding the safety of individuals participating in the research.

9.3.2.5 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.

9.4 Adverse events follow-up

The adverse events which are not related to the tested product(s) or to the protocol are not followed-up. The adverse events/effects susceptible to be in relationship with the tested product(s) or the protocol are followed by the investigator until stabilization or resolution of the symptoms.
If it is required, the investigator can take the decision to prescribe an appropriate treatment to the subject and/or to orientate the subject to an appropriate specialist.
In the frame of this follow-up and according to the investigator's request, some extra visits should be performed by the subject (during the research or after the research termination).

10 DATA HANDLING AND STUDY MONITORING

10.1 Data collection and control

At each visit of the subject, the investigator reports in the source documents the data related to the subject's health state and the safety of the product(s) applied according to the protocol within the study. These data are then reported in the Case Report Form. All data for this study will be recorded on Case Report Forms.

The case report forms will be designed to identify each subject by a subject number and, where appropriate, subject's initials. One Case Report Form must exist for each subject participating in the study. The case report form must be completed legibly, using a black ballpoint pen. Erroneous values and/or text must not be erased. Instead, the error must be crossed out with a single line, the correct value/text added, and the correction signed, initialled and dated by the investigator(s).

The Clinical Research Associate ensures the coherence and the veracity of the data reported in the Case Report Form comparing to the source data and the protocol of the study.

10.2 Clinical monitoring

The monitoring of the study will be done by the CRO Dermscan. The monitor has the responsibility to familiarise the Investigator(s) and the centre staff involved in the study with all study procedures if necessary. The monitor has the responsibility of reviewing the ongoing study with the Investigator(s) to verify adherence to the protocol and to deal with data queries as well as any problems that arise during the conduct of the study.

10.2.1 Monitoring visits

10.2.1.1 Initiation visit

Before any patient's enrolment, the CRA and/or the study monitor will conduct an initiation visit in order to familiarise the centre's staff with the study protocol and schedule.

This visit will also be the occasion to review with the centre:

- the Investigator file which should contain:
  - the Protocol of the study,
  - the curriculum vitae of the Investigator,
  - the Authorisation as a clinical centre, if applicable,
  - the insurance certificate,
  - the favourable opinion of the ethic committee,
  - the approval of CA,
  - the Investigator brochure,
  - the financial agreement between all parts,
  - all necessary documents for study follow-up, etc.
- the CRF and the way to complete it,
- the information sheet and consent forms and the way to obtain consent,
- the investigational product,
- the auxiliary treatment
- the study material (pregnancy test, etc.),
- and all other necessary aspects and materials detailed in the study protocol.

10.2.1.2 Monitoring visits

For the duration of the study, monitoring visits may be performed by the CRA in order to check the study efficacy in accordance with the study protocol.

The Clinical Research Associate ensures the coherence and the veracity of the data reported in the Case Report Form compared to the source data. He/she verifies that the study is performed according to the protocol and that all documentation necessary to ensure a good follow-up of the study is present and well completed.

These visits will also serve to ensure products accountability.

During these visits, the CRA reserves the right to ask for queries resolution, directly in the document(s) concerned or with specific data clarification forms. He/she ensures the completion of the Investigator file and retrieves all documents necessary for updating the trial master file.

When applicable, the CRA may retrieve duplicate of the CRF to be sent to the data management department.

10.2.1.3 Close-out visit

A close out visit will take place after the study has come to a conclusion. The CRA will retrieve all investigational products, auxiliary treatment, materials, CRFs, consent forms (if applicable) and to confirm the completion of the Investigator file, including all study related documents. When necessary, the Sponsor may also ask for the resolution of any delayed queries in the CRFs.

10.2.2 Access to source data

In accordance with good clinical practices and the standards of the data protection law, data obtained in the course of a biomedical research has to be treated confidentially to guarantee the patients' privacy.

The Investigator agrees that, patient to local regulations and ethical considerations, the Sponsor representatives designee and/or and any regulatory agency have direct access to all study records, CRFs, corresponding patient medical records, study drug dispensing records and study drug storage area, and any other documents considered source documentation. The Investigator also agrees to assist the representative, if required.

11 DATA MANAGEMENT

11.1 Procedures used for data review, database cleaning and issuing/resolving data queries

11.1.1 Data entry

The personnel in charge of the study in the centres will record data to paper case report form.
A data entry mask will be created/performed as well as instructions for the data entry.
A double independent data entry will be done from the case report forms by the designed technician(s) or operator(s). The double data entry will be checked by comparison of both entries. A final quality control will be done on a part of the CRFs ($\sqrt{n}+1$).

11.1.2 Data management

Data management will consist in the different following steps:

- Redaction of a data management plan and a data validation plan.
- Redaction of annotated CRF
- Programming and validation of consistency controls
- Data Clarifications Forms (DCFs) emission and database correction
- Data listings emission
- MedDRA coding of AE/ADE and WhoDrug for concomitant medications and validation of the coding by an expert
- Data Management report

11.1.3 Data Review

A study data review will be organised by AdBiostat,

Will be present a minima the sponsor and the statistician and the study monitor.

The study review will aim at determining the analysis population by:

- reviewing the conditions of study's realisation,
- determining the populations for the statistical analyses,
- specifing all the protocol's deviations as major or minor,

- reviewing the statistical analysis plan.

Following the study review, the statistical analysis populations will be defined and a report will be written and validated by AbBiostat and the Sponsor. The database will thus be corrected and locked.

11.1.4 Preparation and lock of the Database

The database will be locked upon resolution of all queries. A copy of the locked database will be sent to the Sponsor. A signed database lock form will be provided.

After the database is locked, any change to the database can only be done from database correction forms approved by the Project Manager and the Sponsor. If the database needs to be corrected, lock/unlock of the database must be clearly documented by the Project Manager in the study file.

11.2 Procedures for verification, validation and securing of electronic clinical data systems, if applicable

If applicable, the CRO will check the electronic data systems of the investigators and the company in charge of data management, according to its internal procedures.

11.3 Procedures for data retention and specifed retention period

The Sponsor must archive the protocol, documentation, approvals and all other essential documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out, for 15 years.

Study centres and/or Dermscan will archive the investigator files and all documents used for data treatment, as detailed below:

- All documents must be archived in a secure place and treated as confidential material.
- Paper documents relating to this study are stored maximum during one year on site before to be transmitted for archiving to an approved service provider.

Data will be archived securely as digital and paper version for 15 years from the date of dispatch of the final report's acceptance.

At the end of this period of 15 years, the study archives could be destroyed.

11.4 Other aspects of clinical quality assurance, as appropriate

In order to ensure the conformity of the studies entrusted to Good Clinical Practices and regulatory requirements, AdBiostat has implemented a quality management system..
This system consists of procedures and quality controls.

12 STATISTICS

The statistical analysis plan (SAP) will provide detailed methods for the analyses outlined below.
Any changes from the planned analyses will be described and justified in the final clinical study report.

12.1 General considerations

The statistical analysis will be performed using SAS software, version 9.2 or later.

The following descriptive statistics will be provided:

- For quantitative variables: number of observed and missing values, mean, standard deviation, minimum, median, maximum
- For qualitative variables: number of observed and missing values, frequencies and percentages per class

The significance level of 0.05 (bilateral) will be applied for statistical tests.

For the variables recorded in both eyes the descriptive analyses will be given separately for the worse eye and the contralateral eye.
The **worse eye** will be defined as follows:

- For patients with both eligible eyes, the worse eye will be:
  Eye with the worse Oxford score;

if same Oxford score in both eyes: eye with the worse Schirmer score;

if same Oxford and Schirmer scores in both eyes: eye with the worse TBUT score;

if same Oxford, Schirmer and TBUT scores in both eyes: right eye.

- For patients with one eligible eye, the worse eye will be the eligible eye.

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

12.2 Analysis sets

The following analysis sets will be considered:

- **Safety set:** All enrolled patients having received at least one dose of IP.
  Safety set will be the primary population for safety analysis.

- **Intent-to-Treat (ITT) set:** All randomized patients.

- **Modified Intent-to-Treat (m-ITT) set:** All randomized patients having received at least one dose of IP, with at least one baseline and one post-randomisation efficacy assessment on treatment.

- **Per protocol (PP) set:** All m-ITT patients without any major protocol violation.
  Deviations from the protocol including violations of inclusion/exclusion criteria will be defined and assessed as “minor” or “major” in cooperation with the sponsor during a data review meeting before the database lock.

12.3 Statistical analyses

12.3.1 Study population

The number of patients in each analysis set will be provided.
Premature discontinuations from the study will be presented.
All baseline characteristics will be described:

- Demographics
- Ocular and systemic medical history

- History of Dry Eye
- Symptomatology evaluation (VAS)
- Ocular symptoms
- Far Best Corrected Visual Acuity (FBCVA) in both eyes
- OSDI score
- Schirmer test
- Slit Lamp examination (TBUT, Oxford 0-15 grading scheme Scale, Van Bijsterveld staining)
- Conjunctival hyperaemia (Mac Monnies photographic scale)

12.3.2 Efficacy Analyses

Efficacy endpoints will be analysed in m-ITT (primary analysis population for the efficacy) and PP.

The primary efficacy criterion is the change in ocular symptomatology assessed on a Visual Analogue Scale (VAS) between D1 and D42.
Estimate of the change and associated 95% confidence interval will be provided, as well as p-value for the paired t-test.

The following parameters will also be analysed:

Secondary endpoints

- Evolution of global ocular staining score according to Oxford 0-15 grading scheme (fluorescein coloration) between D1 and D42
- Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and D42
- Evolution of the soothing sensation assessed by the patient between D1 and D42

Other assessments at D14

- Evolution of the ocular symptomatology on a Visual Analogue Scale (VAS) between D1 and D14
- Evolution of global ocular staining score according to Oxford 0-15 grading scheme (fluorescein coloration) between D1 and D14
- Evolution of Van Bijsterveld score (lissamine green coloration) between D1 and D14
- Evolution of the soothing sensation assessed between by the patient between D1 and D14

Other assessments at D14 and D42

- Evolution of OSDI score (Ocular Surface Disease Index) between D1 and D14 and between D1 and D42
- Evolution of the following Dry Eye symptoms between D1 and D14 and between D1 and D42: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation, light sensitivity graded by the patient.
- Evolution of conjunctival hyperaemia at slit lamp examination between D1 and D14 and between D1 and D42
- Evolution of Schirmer test (without anaesthesia) between D1 and D14 and between D1 and D42
- Evolution of TBUT (Tear Break-Up Time) between D1 and D14 and between D1 and D42
- Global efficacy assessment by the investigator using a 4-point verbal scale at D14 and D42.

12.3.3 Safety Analyses

Safety endpoints will be analysed in the Safety Set.

Safety analysis will be based on the following criteria:

- Ocular symptoms upon instillation: : burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, foreign body sensation, and other symptoms will be graded by the patient.at D14 and D42
- Far best corrected visual acuity assessment at D42
- Global ocular tolerance assessed by the investigator at D42
- Global ocular tolerance assessed by the patient at D42
- Ocular and systemic adverse events (AE)

The adverse events will be coded using the MedDRA dictionary and described according to MedDRA Preferred Term (PT) and primary System Organ Class (SOC).
The number and percentage of patients with at least one adverse event will be summarized for all AEs, study product-related AEs, serious AEs, and AEs leading to study withdrawal.

12.3.4 Pharmacokinetic Analyses

Not Applicable

12.4 Interim Analyses

No interim analysis is planned.

13 ADMINISTRATIVE REQUIREMENTS

13.1 Amendments to protocol

Any modification to the protocol will be treated as a substantial or non-substantial modification, according to its nature, and will be submitted for opinion/approval to the Ethics Committee and/or Competent Authority if applicable.

13.2 Protocol deviations management

All protocol deviations will be managed according to Dermscan Standard Operating Procedure (SOP).

A priori, patients having at least a major deviation and patients with insufficient treatment duration or without any evaluation of main criterion will be excluded from Per Protocol analysis.

Nevertheless, all deviations will be discussed during the data review which will occur before data analysis.

All deviations observed by the CRA during monitoring visits will be reported to Laboratoires Théa in the monitoring report, within maximum 10 days after the visit.
In case of serious GCP and protocol deviations the CRA should report to the CPL of Laboratories Théa by a phone call or writing an email within 24 hours.

At the study end, all deviations will be summarized and analyzed in the data review report, sent to the Sponsor.

If major deviations from an investigator are observed during monitoring, the CRA will warn the investigator of the importance to respect the protocol. An investigator who continuously violates the protocol despite CRA warnings could be excluded from the investigation after agreement of the Sponsor.

13.3 Audit and inspection

The study is conducted under the responsibility of the sponsor in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines, Helsinki Declaration (1996) and in respect of the sponsor and/or CRO SOPs for study conduct and monitoring.

Audits may be carried out by the Sponsor/CRO representatives, and inspection may be performed by regulatory authorities' inspectorate before, during, or after the study. The investigator will allow and assist the CRO/sponsor's representatives and any regulatory agency to have direct access to all study records, CRFs, subject medical records, study drug dispensing records and study drug storage area, study facilities, and any other documents considered source documentation.

For the Audit(s) performed by, or on behalf of, sponsor auditors, audit certificate(s) will be provided to the investigator.

13.4 Quality Control and Insurance

In order to ensure the conformity of the studies entrusted to Good Clinical Practices and regulatory requirements, DERMSCAN has implemented a quality management system which has been certified ISO 9001:2008.
This system consists of procedures and quality controls.

13.5 Final Report

A final report according to ICH E3 will be written by the Laboratoires Théa.
This final report will be signed by the Coordinating Investigator, the Biostatistician and the Sponsor.

13.6 Insurance

The sponsor has subscribed an insurance contract to cover the liability of the investigators, the sponsor himself and anyone involved in the study.
The copy of the insurance certificate is presented separately in the EC and CA submission file.

13.7 Publications policy

The sponsor reserves the right to review all the manuscript(s) and abstract(s) before their submission for publication or presentation. Publication of data will be at the discretion of the sponsor

This is not intended to restrict or hinder publication or presentation, but to allow the sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator(s).

14 ETHICS CONSIDERATIONS

Declaration of HELSINKI[(1)]

The current revision of the Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol. Independent assurance that patients are protected can only be provided by an ethics committee/institutional review board and freely obtained informed consent.

Good Clinical Practice[(2)]

Good clinical practice is a standard for clinical studies, which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures the studies are ethically justified and scientifically sound, and that the clinical properties of the diagnostic/therapeutic/prophylactic product under investigation are properly documented.
It is the responsibility of the investigator(s) to ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.

Ethics Committee and Competent Authority[(3)]

It is the responsibility of the sponsor or its legal representative to submit a copy of the protocol and detailed patient information sheet and consent form to an ethics committee/institutional review board in order to obtain independent approval to conduct the study. Ethics committee/institutional review board approval

must be obtained before the study is started. The approval of the ethics committee/institutional review board must be sent in writing, to the sponsor or its legal representative. The Ethics Committee approval letter must mention the Ethics Committee members and their function.
In parallel or after the Ethics Committee submission, the sponsor or its legal representative must address an authorization request to the Tunisian authorities.
Any clinical trial cannot been performed without having obtained the agreement of the Ethics Committee and the inherent authorization of the Tunisian authority.

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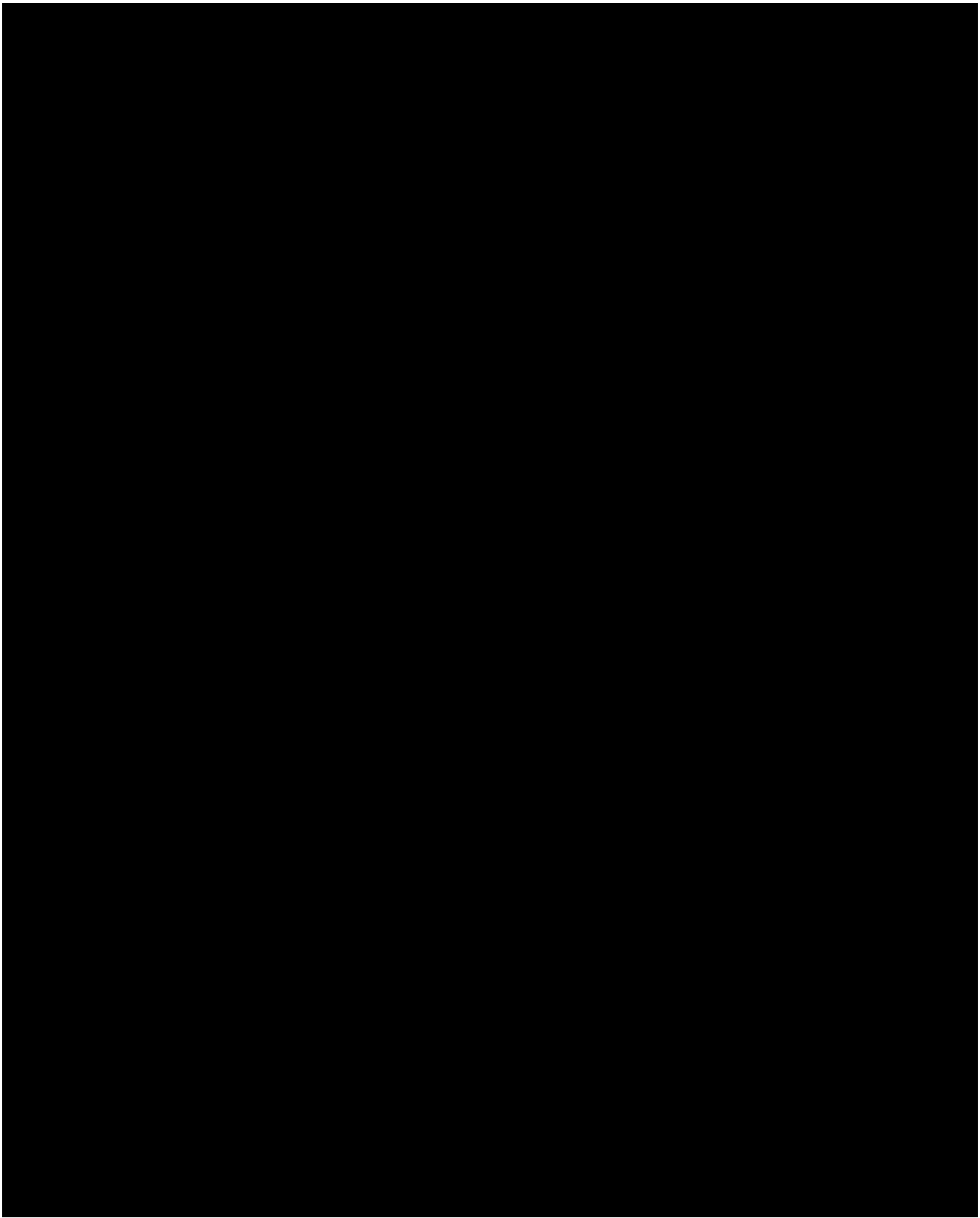
16 SIGNATURE (S) OF THE PROTOCOL

We agree to conduct the study in accordance with the study protocol described in this document and in compliance with GCP and applicable regulatory requirements.



FOR THE COORDINATING INVESTIGATOR:

[redacted]

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and understood the protocol. I agree to meet all the obligations and restrictions outlined for me in the protocol. I will obtain written informed consent from all study participants prior to conducting any study procedures. All information regarding this protocol and the study product will be treated as strictly confidential. I will conduct the study in all respects in accordance with the study protocol and the ethical principles of the current version of the declaration of Helsinki and GCP.

SPONSOR: LABORATOIRES THÉA

[redacted]

_____	_____	_____
Name / surname	*date*	*signature*

_____	_____	_____
Name / surname	*date*	*signature*

Appendix 1: McMonnies Scale