1 GENERAL

1.1 IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN (CIP)

1.1.1 Clinical Investigation References

CLINICAL INVESTIGATION PLAN

Investigation No. LT2769-003

NCT Number: NCT05931861

Date of the initial Clinical Investigation Plan: 04-MAY-2023

Version of the initial Clinical Investigation Plan: 1.0

1.1.2 CIP Amendments

Amendment N#: NA Version of the Amended CIP: NA			
Section number	**Section Name**	**Changes description**	**Rationale or justifications**
NA	NA	NA	NA

TITLE: Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms.

LABORATOIRES THÉA

Clinical Investigation Plan (CIP) No.:	LT2769-003
Investigational Medical Device (IMD):	T2769
Intended purpose:	To hydrate and soothe itchy, red or irritated eyes
Coordinating Investigator:	PPD , MD, PhD
Sponsor's Medical Expert:	PPD , MD

1.1.3 Abbreviations and Acronyms

ADDE	Aqueous Deficient Dry Eye
ADE	Adverse Device Effect
AE	Adverse Event
ALCOACCEA	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available
ATC	Anatomic Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BSA	Biological Safety Assessment
CA	Competent Authority
CI	Confidence Interval
CIP	Clinical Investigational Plan
CIR	Clinical Investigational Report
CL	Contact Lens
CLADE	Contac Lens-Associated Dry Eye
CLD	Contact Lens Discomfort
CLDEQ	Contact Lens Dry Eye Questionnaire
CLIDE	Contact Lens-Induced Dry Eye
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
CRO	Contract Research Organisation
e-CRF	Electronic Case Report Form
DD	Device Deficiency
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
DMP	Data Management Plan
EDE	Evaporative Dry Eye
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions For Use
IMD	Investigational Medical Device
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
m-ITT	Modified Intent-to-treat
NA	Not Applicable
OSDI	Ocular Surface Disease Index
PI	Principal Investigator

PP	Per Protocol
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
RMP	Risk Management Plan
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDR	Source Data Review
SDV	Source Data Verification
SH	Sodium Hyaluronate
SOC	System Organ Class
SOTA	State of the Art
TBUT	Tear Break Up Time
TFOS	Tear Film & Ocular Surface Society
TEAE	Treatment Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

1.2 SPONSOR

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First Name - Name/function	Details
PPD	Email: PPD
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	Email: PPD
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	Email: PPD

1.3 PRINCIPAL INVESTIGATOR, COORDINATING INVESTIGATOR AND INVESTIGATION SITE(S)

1.3.1 Investigators Details

The Sponsor will maintain an updated list of Principal Investigator (PI), and investigation site(s), separately from this CIP, throughout the duration of the clinical investigation. The definitive list will be provided with the Clinical Investigation Report (CIR).
Roles, responsibilities, and qualifications of investigators are detailed in the CIP.

1.3.2 External Organizations Details

STATEMENT OF THE SPONSOR AND OF THE COORDINATING INVESTIGATOR

Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms.

The information contained in this CIP is consistent with:

- The current risk-benefit evaluation of the IMD
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki - October 2013, Good Clinical Practice (GCP) as described in the ISO 14155 current version.

The investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the IMD.

COORDINATING INVESTIGATOR

First Name - Name	*date*	*signature*

SPONSOR: LABORATOIRES THÉA

PPD *First Name - Name*	*date*	*signature*
PPD *First Name - Name*	*date*	*signature*
PPD *First Name - Name*	*date*	*signature*

INVESTIGATOR SIGNATURE PAGE

Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms.

The signature below:

- Confirms my agreement to conduct the investigation in compliance with GCP – ISO 14155 current version, Medical Device Regulation (MDR 2017/745), other applicable regulatory, and the CIP requirement(s).
- Confirms my agreement to comply with procedures for data recording/reporting.
- Confirms my agreement to permit monitoring, auditing, and regulatory inspection.
- Confirms my agreement to retain the essential documents of this clinical investigation in the investigator files until Laboratoires THÉA informs me that these documents are no longer needed (*e.g.,* at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market).
- Ensure that all people assisting with the clinical investigation are adequately informed about the CIP, the IMD(s) and their trial-related duties and functions.
- Confirms that I have read this CIP and that I agree to comply with all parts or items.

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

INVESTIGATIONAL SITE

Principal Investigator

_____	_____	_____
First Name - Name	*date*	*signature*

SPONSOR: LABORATOIRES THÉA

PPD

PPD	_____	_____
First Name - Name	*date*	*signature*

1.4 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Title	**Performance and safety assessment of T2769 in contact lens wearers with dry eye symptoms.**
Sponsor	Laboratoires THÉA
Sponsor Investigation No.	**LT2769-003**
Investigation Centre(s)	This investigation is planned to be carried out at approximately 6 sites in European Union (EU).
Planned Schedule	Planned initiation: August 2023 Planned last patient last visit: January 2024
Primary Investigation Objective	To assess the performance of T2769 in contact lens wearers with dry eye symptoms in terms of change from baseline (Day 1) to Day 36 (Final visit) in Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) total score.
Secondary Investigation Objective(s)	To assess the performance and safety of T2769 in contact lens wearers with dry eye symptoms.
Sample Size	CCI evaluable patients
Investigation Design	A prospective, single-arm, multicenter, 5-week investigation. Three visits: Visit #1: Day 1 Inclusion visit (D1) Visit #2: Day 15 (±1 day) (D15) Visit #3: Day 36 (+3 days) Final visit (D36) All visits must take place in the afternoon.
Investigation Duration	▪ Treatment period: 36 +3 days Total investigation duration: maximum of 39 days
Investigational Medical Device (IMD)	**Formulation:** T2769: sodium hyaluronate 0.15%, Trehalose 3%, Naaga 2.45% in a 12.5 mL ABAK® multi-dose bottle. **Route of administration:** Topical, by ocular route **Dose regimen:** 1 drop in each eye, from 3 to 6 times daily, at any time but only when patients are wearing their contact lenses.

Inclusion Criteria	1.1. Informed consent signed and dated (obtained prior to initiating any procedures). 1.2. Patient aged ≥ 18 years old. 1.3. Well fitted contact lenses (CL) according to the investigator judgement. 1.4. Daily wearer of any type of CL for a minimum of 5 days/week for 6 hours/day over at least the last month and is willing to continue to do so during the study. 1.5. Patient with an Ocular Surface Disease Index (OSDI) score ≥ 18. 1.6. CLDEQ-8 score ≥ 12. CCI [redacted]
Exclusion Criteria	**<u>Ophthalmic Exclusion Criteria in AT LEAST ONE EYE</u> [2.1]** 2.1.1. Far Best-Corrected Visual Acuity (BCVA) ≥+0.7 LogMar (e.g., ≤0.2 in decimal value or ≤20/100 Snellen equivalent or ≤50 ETDRS letters). 2.1.2. Severe blepharitis according to the judgment of the investigator. 2.1.3. Confirmed diagnosis of severe Meibomian gland dysfunction. 2.1.4. Presence of palpebral or nasolacrimal disorders. 2.1.5. Dry eye associated with at least one of the following diseases/symptoms: – Ocular rosacea, – Pterygium, – Eyelid malposition, – Corneal dystrophy, – Ocular neoplasia, – Filamentous keratitis, – Corneal neovascularisation, – Orbital radiotherapy, – Cataract, – Retinal disease. CCI [redacted]

Exclusion Criteria (continued)	CCI [redacted]
Exclusion Criteria (continued)	

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

Patient Withdrawal	The investigator may choose to discontinue a patient for the following reasons: - Any safety reason(s)/Adverse Event(s) (AEs) necessitating discontinuation from the investigation, - Any abnormality with IMD, - Lack of performance: if the patient or the investigator does not feel that the IMD has sufficiently controlled the pathology/has adequately relieved his/her symptoms, - Patient compliance, - Patient's request, - Any exceptional circumstance (e.g., COVID-19 pandemic), - Other reasons. In the case of discontinuation, the patient will be withdrawn from the investigation and the investigator will prescribe him/her the best appropriate treatment if needed.
Performance Parameters	• CLDEQ-8 self-questionnaire. • Soothing sensation just after IMD instillation (less than 5 minutes) using a 4-point scale. • OSDI self-questionnaire. • Ocular discomfort within the last 48 hours on a Visual Analog Scale (VAS, 0-100) (from 0 [no discomfort] to 100 [maximal discomfort]). • Ocular symptoms throughout the day within the last 48 hours: burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation, graded using a 4-point scale. • Contact lens wearing time (hours/day and days/week). • Conjunctival hyperaemia using Mc Monnies photographic scale (0-5) in each eye. • Tears Break Up Time (TBUT) in each eye (in sec). • Total Ocular surface staining according to Oxford 0-15 grading scheme (corneal and conjunctival staining by fluorescein with a yellow filter) in each eye. • Schirmer test (without anesthesia) in each eye (in mm/5 min). • Performance assessment by the investigator using a 4-point scale (very satisfactory, satisfactory, not very satisfactory, unsatisfactory).
Safety Parameters	• Ocular AE reporting. • Systemic AE reporting. • Reporting of Device Deficiencies (DD) that may lead to Serious Adverse Event (SAE). • Far BCVA in each eye. • Ocular tolerance assessed by the investigator using a 4-point scale (very satisfactory, satisfactory, not very satisfactory, unsatisfactory). • Ocular tolerance assessed by the patient using a 4-point scale (very satisfactory, satisfactory, not very satisfactory, unsatisfactory).
Primary Performance Endpoint	The primary performance endpoint is the change from baseline[a] (D1) to D36 in the CLDEQ-8 total score*.
Secondary Performance Endpoints	• Change from baseline[a] (D1) in CLDEQ-8 total score* at D15. • Soothing sensation just after instillation (less than 5 minutes)* at D15 and D36.

	• Change from baseline[a] (D1) in OSDI* total score at D15 and D36. • Change from baseline[a] (D1) in the ocular discomfort score on the VAS* at D15 and D36. • Score of each ocular symptom throughout the day* (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation) at D15 and D36 and change from baseline[a] in the total score of these symptoms. • Change from baseline[a] (D1) in contact lens wearing time at D15 and D36. • Change from baseline[a] (D1) in conjunctival hyperaemia score at D15 and D36 separately in the studied eye[b] and in the contralateral eye. • Change from baseline[a] (D1) in TBUT at D15 and D36 separately in the studied eye[b] and in the contralateral eye. • Change from baseline[a] (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D15 and D36 separately in the studied eye[b] and in the contralateral eye. • Change from baseline[a] (D1) in Schirmer test result (without anesthesia) at D15 and D36 separately in the studied eye[b] and in the contralateral eye. • Performance assessment by the investigator at D15 and D36. [a]baseline is defined as the assessment at inclusion visit before the first IMD instillation. Missing value at inclusion visit will not be replaced. [b]defined in the statistical considerations section. *Patient questionnaire
Safety Endpoints	• Treatment-Emergent Adverse Event (TEAE) by System Organ Class and Preferred Term (separately for ocular and systemic TEAE). • Change from baseline in Far BCVA expressed in Log MAR at D36 separately in the studied eye and in the contralateral eye. • Ocular tolerance assessed by the investigator at D15 and D36. • Ocular tolerance assessed by the patient at D15 and D36.
Statistic Considerations	**<u>Determination of Sample size</u>** This is a confirmatory clinical investigation. The objective is to collect new additional clinical data demonstrating the safety and performance of the device in the contact-lens wearing population with dry eye symptoms. Consequently, no formal sample size calculation is performed, and it is considered that around evaluable CCI patients is sufficient to reach the study objectives. A total of CCI patients should be enrolled in the study to take into account approximately 10% of non-evaluable patients. **<u>Analysis sets</u>** The following analysis sets will be considered: • **Safety set:** All enrolled patients, having received at least one instillation of IMD. The safety set will be the primary population for safety analysis. • **Full-Analysis Set (FAS):** All enrolled patients having received at least one instillation of IMD. The FAS will be the primary population for performance analysis.

	• **Per protocol (PP) set:** Subset of the FAS including patients without any major CIP violations likely to seriously affect the primary outcome of the study. Deviations from the CIP will be defined and assessed as "minor" or "major" in cooperation with the sponsor during a data review meeting before the database lock. The PP set will be considered as secondary population and will be used for sensitivity analyses of the primary and secondary endpoints.
	CCI [redacted]
	Quantitative variables (Continuous data) will be summarized in summary tables indicating the number of non-missing observations (n), mean, Standard Deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% Confidence Interval (CI) of the mean/median. Qualitative variables (Categorical data) will be summarized in summary tables indicating the number of non-missing observations (n), count and percentage of each modality, and 95% CI. Baseline is defined as the assessment at D1 visit before the first IMD. Missing value at inclusion visit will not be replaced. For endpoints defined as change from baseline (D1), the descriptive statistic by visit and the change from baseline will be presented. Statistical tests will be described in the statistical section of the CIP.
	No Interim analysis is planned.
Schedule of Assessments	Please refer to the **Table 2 Schedule of Visits and Procedures**.

Table 2 Schedule of Visits and Procedures

	Visit#1 Inclusion Visit *(D1, afternoon)*	Visit#2 *D15 (±1 day), afternoon* [(1)]	Visit#3 Final visit[(1)] *D36 (+3 days), afternoon* **or premature discontinuation visit**[(2)]
Informed consent	X		
Demography	X		
Contact lens history	X		
Ocular and Systemic Medical and Surgical History (including dry eye)	X		
Previous and Concomitant Ocular/Non-ocular Treatments	X	X	X
CLDEQ-8 self-questionnaire [(3)]	X	X	X
Soothing sensation just after (less than 5 min) IMD instillation [(3)]		X	X
OSDI self-questionnaire [(3)]	X	X	X
Ocular discomfort evaluation (VAS) [(3)]	X	X	X
Ocular symptoms throughout the day [(3)]	X	X	X
Contact lens wearing time	X	X	X
Far Best Corrected Visual Acuity (BCVA) [(4)]	X		X
Slit Lamp Examination[(4)]	X	X	X
Conjunctival Hyperaemia (Mc Monnies photographic scale) [(4)]	X	X	X
TBUT [(4)]	X	X	X
Oxford 0-15 grading scheme (corneal and conjunctival staining by fluorescein with a yellow filter) [(4)]	X	X	X

	Visit#1 Inclusion Visit *(D1, afternoon)*	Visit#2 *D15 (±1 day), afternoon* [1]	Visit#3 Final visit[1] *D36 (+3 days), afternoon* **or premature discontinuation visit**[2]
Schirmer Test (without anaesthesia) [4]	X	X	X
Adverse Events		X	X
Device deficiency		X	X
Urine Pregnancy Test	X		X
Verification of Inclusion and Exclusion Criteria	X		
Ocular tolerance assessment by the patient [3]		X	X
Ocular tolerance assessment by the investigator [4]		X	X
Performance assessment by the investigator [4]		X	X
Training of the patient for diary completion	X	X	
Patient diary dispensation	X	X	
IMD Dispensation	X		
IMD Compliance / Patient diary completion review		X	X
Record of used/unused IMDs (in Treatment Kit Tracking Form)			X

1) No IMD instillation at least 2 hours before visit#2 and visit#3.
2) If premature discontinuation, **also** collect the new treatment for the dry eye (if applicable) with the start date and the dosing.
3) These questionnaires and VAS must be answered by the patient at the beginning of the visit (before examination).
4) Ophthalmological examinations and assessments **MUST** be performed by the **SAME** investigator.

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CCI

[redacted]

2 IDENTIFICATION AND DESCRIPTION OF THE IMD

2.1 SUMMARY DESCRIPTION OF THE IMD AND ITS INTENDED PURPOSE

The patient will be trained for the correct instillation technique of IMD. The patient will be provided with an information on the informed consent form, on the labels on the IMD boxes and with instruction for use in local language.

Test device: T2769

T2769 (THEALOZ TOTAL) is a sterile, phosphate-free and pH neutral solution. It contains Trehalose, Sodium Hyaluronate (SH) and Naaga.
T2769 device is presented in the ABAK® III multi-dose bottle (12.5 mL).
As per Instructions for Use (IFU), T2769 is indicated in case of moderate to severe dry eye syndrome.

2.2 DETAILS CONCERNING THE MANUFACTURER OF THE IMD.

The legal manufacturer of T2769 according to the European Union (EU) Medical Device Regulation (MDR) 2017/745 is Laboratoires THÉA.

The site responsible for manufacturing/packaging/control/release of the finished product is:
FARMILA-THEA Farmaceutici S.p.A: Via E. Fermi, 50, 20019 Settimo Milanese, ITALY.

The IMD was manufactured in accordance with Good Manufacturing Practices (GMP).

2.3 NAME OR NUMBER OF MODEL/TYPE, INCLUDED SOFTWARE VERSION AND ACCESSORIES, IF APPLICABLE, ALLOWING A FULL IDENTIFICATION

Not Applicable.

2.4 PACKAGING AND LABELLING

2.4.1 Packaging

The IMD will be packaged by approved contractor in accordance with ISO 14155 current version and European Union (EU) Medical Device Regulation (MDR) 2017/745.

T2769 is packaged in a multidose white polyethylene ABAK® III system bottle. The dispenser is already used in several currently marketed eye drops. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution without the use of any preservatives:

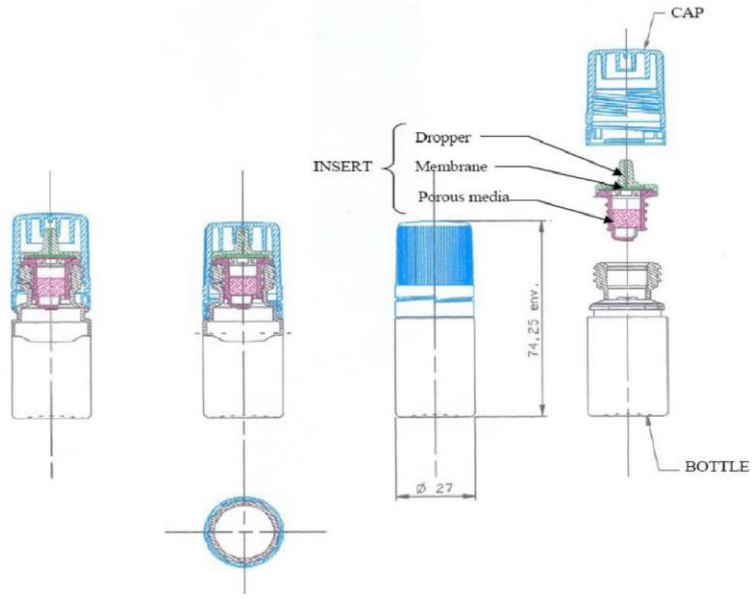

Figure 1. Diagram of the ABAK® III bottle

The complete treatment for one patient and for the complete investigation duration will be as following:

Packaging	T2769
	Visit 1 to Visit 3 period (Day 1 to Day 36)
Primary (I)	2 vials
Final	1 cardboard carton

Thus, each patient will receive 2 preservative-free multidose bottles of the IMD during the investigation.

2.4.2 Labelling

All labels will be written in the local language. The content of the labelling is in accordance with ISO 14155 current version and European Union (EU) Medical Device Regulation (MDR) 2017/745 specifications and requirements.

Each vial of IMD will carry one label.

The cardboard carton will also carry a detachable label (flag label) bearing at least the CIP number and IMD kit number. This label will be torn off by the person dispensing the IMD to the patient and will be stuck in the space provided in the IMD allocation form to record the dispensing procedure.

2.5 INTENDED PURPOSE OF THE IMD IN THE PROPOSED CLINICAL INVESTIGATION

T2769 is intended to hydrate and soothe itchy, red or irritated eyes.

2.6 THE POPULATIONS AND INDICATIONS FOR WHICH THE IMD IS INTENDED

T2769 is indicated in moderate to severe dry eye syndrome. T2769 is suitable for adults, including wearers of any type of contact lenses.

2.7 DESCRIPTION OF THE IMD

T2769 is an ophthalmic solution composed of trehalose (3%), sodium hyaluronate (0.15%), N-Acetyl Aspartyl Glutamic Acid Sodium salt (Naaga, 2.45%), sodium hydroxide (for pH adjustment) and water for injections.

The solution is supplied in the ABAK® III multi-dose bottle. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution without the use of any preservatives.

The product can be used until 3 months after first opening.

Table 3 Investigational Medical Device T2769

CCI

The excipients of the T2769 eye-drops (NaOH, water for injections) are well-known and commonly used in ophthalmic formulations.

Batch number and expiry dates will be provided in the certificate of analysis and will be specified on the packaging.

2.8 STORAGE CONDITIONS AND INDICATIONS OF USE

All IMD should be stored in its original packaging, protected from light and moisture, at a temperature between 8 and 25°C and the expiry date refers to the last day of that month as long as the packaging is intact, and it has been stored correctly.

The IMD must not be used if the vial is damaged and must not be refrigerated or frozen.

Until dispensed to the patient, products should be in a secure area with restricted access. The investigator, the hospital pharmacist or other personnel allowed to store and dispense IMD(s) will be responsible for ensuring that the IMD(s) are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

T2769 should not be used after the expiry date indicated on the outer cardboard box. The expiry date refers to the intact correctly stored packaging.

The product can be used until 3 months after first opening.

If significant changes and/or update on labelling, handling and storage are required during the clinical investigation, the corresponding sections will be updated by notifying or submitting to Competent Authorities (CAs) concerned accordingly. All investigators' sites will be immediately informed about any change by the Sponsor, investigator or a delegate will inform the patient, if any.

Accordingly, the Sponsor may decide to halt temporary the recruitment (see Section 16.1). In any way, the reasons and the procedures for any changes will be justified and described by the Sponsor.

2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE IMD

Not Applicable

2.10 INVESTIGATOR BROCHURE (IB) AND INSTRUCTIONS FOR USE (IFU)

All details concerning the IMD are specified in separate documents as the IB and the IFU. These documents will be updated whenever necessary and all applicable versions will be provided to each investigation site throughout the clinical investigation.

At time of CIP writing, validated and applicable versions are:

- For the IB: V3, MAR-2023,
- For the IFU: Ver. 8-clin 03/2023.

2.11 DESCRIPTION OF COMPARATIVE DEVICE

Not Applicable

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 BACKGROUND

Dry eye disease (DED) affects millions of people throughout the world and is one of the most common reasons for patients to seek eye care. As defined by TFOS (Tear Film & Ocular Surface Society) Dry Eye Workshop (DEWS) II (Craig et al. 2017):

"Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".

The pathological process of DED is propagated by a chain of events that lead to ocular surface damage. Initially, this gives rise to ocular symptoms and compensatory responses, but it also generates inflammatory responses that ultimately lead to chronic ocular surface damage and self-perpetuate the disease. The vicious circle of dry eye may be initiated by tear hyperosmolarity but also by different disorders such as ocular surface inflammation due to allergic eye disease, topical preservative toxicity, and xerophthalmia which is associated with a loss of conjunctival goblet cells or altered mucin expression (Bron et al. 2017).
Two predominant and non-mutually exclusive categories of DED are Aqueous Deficient Dry Eye (ADDE) and Evaporative Dry Eye (EDE). ADDE describes conditions affecting the lacrimal gland function, while EDE is understood to occur with conditions affecting the eyelid (e.g., Meibomian Gland Dysfunction [MGD] and blink abnormalities) or the ocular surface (e.g., related to mucin deficiency or contact lens wear).
Large epidemiologic studies confirm that female sex and older age increase the risk for DED. Other substantiated risk factors include MGD, hematopoietic stem cell transplantation, computer use, Asian race, contact lens wear, environmental conditions (e.g., pollution, low humidity), Sjögren syndrome, systemic connective diseases, certain classes of medications (e.g., antihistamines, antidepressants, anxiolytics and isotretinoin), and possibly androgen deficiency (Stapleton et al. 2017). Dry eye is currently estimated to affect between 5% to 35% of adults worldwide (Baudouin et al., 2017).
Regardless of the initiating mechanisms and aetiology, the clinical consequences of DED are the same at the ocular surface. These may include punctate epitheliopathy, filamentary keratitis, superior limbic keratitis, goblet cell loss, modification of the epithelial glycocalyx, lid parallel conjunctival folds, changes to Marx's line and MGD itself (Bron et al. 2017).
Both discomfort and visual disturbance symptoms remain fundamental to DED. It causes irritation and pain, and affects ocular and general health and well-being, the perception of visual function and performance. Pain associated with DED can have psychological and physical impacts, while blurred vision may impose restrictions on daily life activities such as reading, driving, watching television and operating smartphones (Stapleton et al. 2017). However, some DED patients exhibit signs of ocular surface disease but report no symptoms of discomfort at the early stage of DED or later stages due to reduced corneal sensitivity (Craig et al. 2017). Moreover, the cost of DED treatment and the chronicity/intractability of DED symptoms affect the social life of an individual (Stapleton et al. 2017).

3.1.1.1 *Contact lens-related DED*

Use of contact lenses (CL) is considered a risk factor for dry eye in several epidemiological studies on dry eye. According to TFOS CLD workshop in 2013, dry eye is a common condition that affects contact lens wearers, with an estimated prevalence ranging from 28-50.4%. It is characterized by ocular discomfort/Contact Lens Discomfort (CLD), dryness, redness, and

itching, and can cause reduced vision and ocular pain. It is caused by decreased tear film stability due to tear film evaporation, meibomian gland dysfunction, lid margin abnormalities, and decreased tear production (Dumbleton et al. 2013).

Although dry eye symptoms have been identified in CL wearers, objective signs must be demonstrated to confirm the existence of DED. In the DEWS II (Gomes et al. 2017), two definitions of dryness related to CL wear were proposed to assist the ongoing interpretation of the literature:

1. CL-Induced Dry Eye (CLIDE): the existence of signs and symptoms of dry eye during CL wear, whereby such signs and symptoms did not exist prior to CL wear.
2. CL-Associated Dry Eye (CLADE): the existence of signs and symptoms of dry eye during CL wear, whereby DED observed in CL wearer could be due to pre-existing dry eye condition.

While millions of people worldwide benefit from CL, a large percentage of wearers experience discomfort at least occasionally (Pucker 2020). The international workshop on contact lens discomfort has defined CLD as:

"A condition characterised by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear (Nichols et al. 2013)."

CLD limits CL wearing time, and in many instances, eventually results in discontinuation. CL dropout was frequent across developed countries, with a frequency ranging from 12.0% to 27.4%. The top cited reason for CL dropout in established CL wearers was discomfort (Pucker et Tichenor 2020).

CLD is primarily reported according to symptomatology as opposed to the observation of signs. While the precise aetiology of CLD is yet to be determined, the use of symptoms as outcome measures is appropriate because it relates directly to the patients' experience with contact lenses and the motivation to seek and use treatment, regardless of the presence of observable signs. The frequency and intensity with which these symptoms are reported can be assessed with the use of questionnaires. The first questionnaire developed specifically to assess symptoms in contact lens wearers was the Contact Lens Dry Eye Questionnaire (CLDEQ). More recently, a short version of the CLDEQ has been developed, the CLDEQ-8. The scores from the CLDEQ-8 have been shown to evaluate the severity of dry eye symptoms in soft contact lens wearers within the past 2 weeks and correlate well with baseline CLD status (Dumbleton et al. 2013).

3.1.1.2 *Treatment options*

The management of DED is multi-factorial and requires an individualised approach (Jones et al. 2017). Lid hygiene and warm compress, non-preserved ocular lubricants are the first-line treatment. In addition, lifestyle modifications such as environmental changes and dietary modifications may also be recommended. Lubricants can be in the form of artificial tears, gels, or ointments and are used to supplement the tear film and provide relief from symptoms. Anti-inflammatory agents, such as corticosteroids, immunomodulators, and cyclosporine, can reduce inflammation and improve tear production. Occlusion therapy, such as punctal plugs or bandage contact lenses, can help to reduce tear evaporation. In some cases, treatments such as eyelid surgery, autologous serum eyedrops, or even scleral lenses may be necessary.

Management options for contact lens-related dry eye include change of care solution, adjust replacement frequency, change of lens design, fit and/or material, tear supplementation (e.g., wetting/lubricating drops), punctal occlusion topical medications (e.g., cyclosporine,

corticosteroids), and improvement of the environment (Papas et al. 2013). Note that anti-inflammatory treatment is conducted to suppress the ocular surface inflammation caused by the friction between the contact lens and keratoconjunctival epithelium (Kojima 2018).

3.2 EVALUATION OF RELEVANT PRE-CLINICAL DATA

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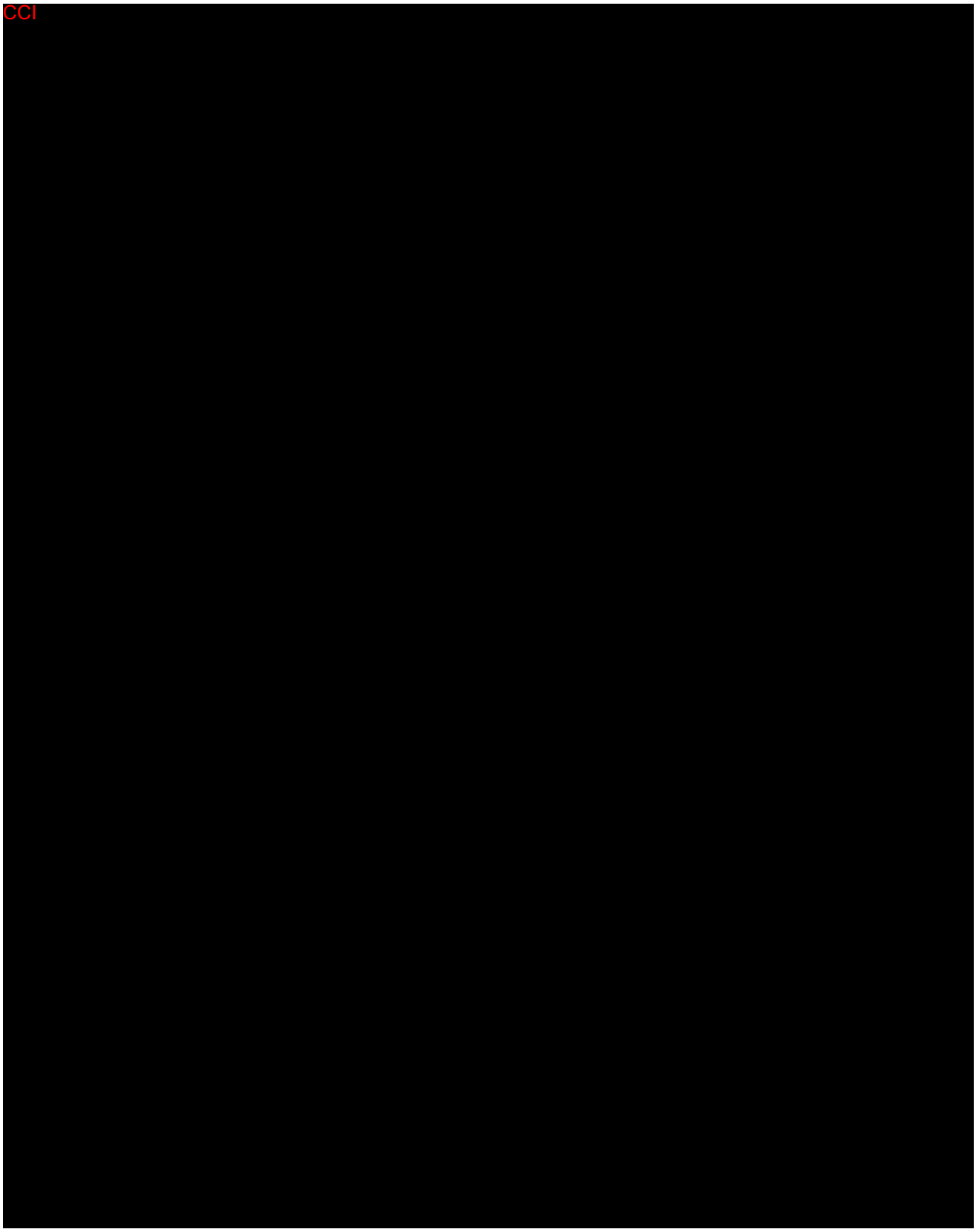

3.3 EVALUATION OF RELEVANT CLINICAL DATA

Clinical performances, safety and benefits on T2769

CIR LT2769-001/17E1044, 24-OCT-20

One clinical investigation on THEALOZ TOTAL (D01) was conducted by Laboratoires THEA (CIR LT2769-001/17E1044).

This clinical investigation was a multicentre, open-label, non-comparative clinical trial (Level of Evidence IIc). It was conducted in Tunisia in 3 sites between 12-October-2018 and 18-February-2019. The primary objective of the clinical investigation was to assess the performance of THEALOZ TOTAL in patients with moderate to severe DES, as well as to assess the safety of the product. During the study, 63 patients were enrolled, and 62 patients were treated for 42 ± 5 days. Patients were adults and did not wear contact lenses. The primary analysis was carried out on the modified Intent-To-Treat (m-ITT) population (all enrolled patients having received at least one dose of product and with at least one baseline and post-baseline performance assessment).

Enrolled dry eye patients were on treatment with artificial tears for at least 3 months before entry in the clinical investigation (screening). After a wash out period of one week during which patients received preservative-free 0.9% NaCl eye drops, patients were treated using THEALOZ TOTAL in ABAK container, administered as one drop in each eye, 3 to 6 times a day for 42 days.

Ocular symptoms of DED were markedly and significantly improved following the administration of THEALOZ TOTAL compared to baseline. All performance criteria were greatly improved, especially ocular symptoms (a great majority of patients had no more symptoms or presented with mild symptoms at the end of treatment). The improvement was rapidly observed after 14 days of treatment with a maximal effect obtained after 42 days of treatment. Also, ocular signs such conjunctival hyperaemia, corneal staining and conjunctival staining were significantly improved. The soothing sensation associated with the use of THEALOZ TOTAL was judged as important by the majority of patients (82.3%) at D42. Some patients normalized their TBUT and/or Schirmer test value. Interestingly, at the end of the clinical investigation, parameters assessed during screening (ocular symptomatology on a VAS, total score of ocular symptoms, global ocular staining, Van Bijsterveld score, conjunctival hyperaemia, TBUT) were improved compared to the screening visit (i.e. before the wash-out period, at the end of the treatment with previous artificial tears).

THEALOZ TOTAL was well tolerated when instilled as 3 to 6 drops daily for 42 days. Ocular symptoms upon instillation (mainly burning/irritation and stinging/eye pain) were noted at the beginning of treatment in less than 20% of patients, but were generally mild, lasting a few minutes.

3.4 DESCRIPTION OF THE CLINICAL DEVELOPMENT STAGE

The investigation is defined as a pre-market, pilot stage (cf ISO 14155:2020). The clinical investigation design is confirmatory.

4 BENEFITS AND RISKS OF THE IMD, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFITS

The following clinical benefits are expected with the use of T2769:

- Improvement of (global) ocular comfort and relief from the symptoms of dry eyes,
- Soothing of ocular sensations (from itchiness and irritations),
- Reduction of the redness of the eyes,
- Good level of tolerance on the eye.

4.2 ANTICIPATED ADVERSE DEVICE EFFECTS

No adverse events related to the use of THEALOZ TOTAL were reported during the clinical investigation LT2769-001.

Based on ocular lubricants recognised adverse events and complications identified within this State of the art, as well as adverse events and complications reported as related to the use of similar devices/products, i.e., THEALOZ DUO and NAAGA-based eye drops, it is possible that THEALOZ TOTAL may be associated with:

- Blurred vision upon instillation (related to THEALOZ DUO),
- Irritation/burning/stinging sensation upon instillation (related to THEALOZ DUO),
- Eye irritation (related to THEALOZ DUO),
- Ocular redness (related to THEALOZ DUO),
- Burning and stinging sensations upon instillation (related to NAAGA).

4.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

Laboratoires THÉA performed a risk analysis according to the current ISO 14971 standard.

All risks identified in Laboratoires THÉA's risk analysis were mitigated. The remaining residual risks were considered to be of negligible or acceptable levels. The risks mitigated to this latter risk level (acceptable) are described in section 4.5.

All the possible warnings have been put in place in the instructions for use as well as on the secondary and primary packaging if possible.

These hazards cannot arise in the normal conditions of use.

4.4 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

To avoid possible interactions with a concomitant treatment, patients will be asked to wait at least 15 minutes between using two different eye products.

4.5 CONTROL AND MINIMISATION OF RISKS

According to the steps defined in the Risk Management Plan (RMP) established for T2769, all identified risks meet the acceptability criteria defined by ISO 14971.

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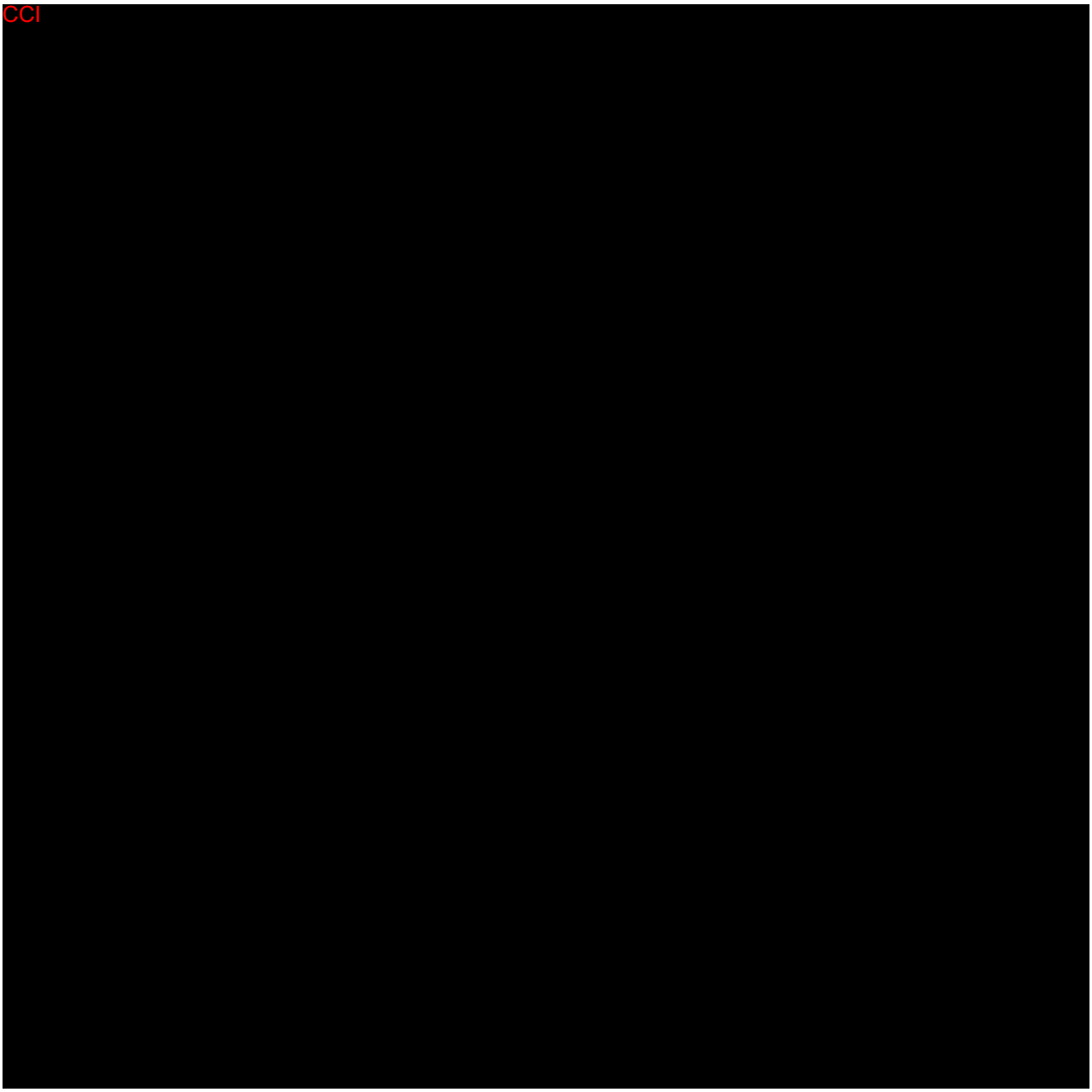

4.6 RATIONALE FOR BENEFIT-RISK RATIO

Based on the current Clinical Evaluation which included data from the State of the Art (SOTA) and clinical data on the IMD), Risk Management documentation and other documentation provided by Laboratoires THEA, it is demonstrated that any risks which might be associated with the use of THEALOZ TOTAL are acceptable when weighted against the benefits to the patient.

This allows the consideration that the benefit/risk ratio is acceptable for THEALOZ TOTAL when used in accordance with its intended purpose in its target treated population, as long as intended users are appropriately informed about known limitations and risks associated with the use of such device.

5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 CLAIMS FOR CLINICAL PERFORMANCE, EFFECTIVENESS OR SAFETY OF THE IMD

There is no claim concerning the clinical performance of THEALOZ TOTAL in the IFU. However, the following clinical performances support the claimed clinical benefits:

- THEALOZ TOTAL reduces ocular surface damages.
- THEALOZ TOTAL increases tear film stability/quantity.

As per the IFU, the claim on clinical safety is:

- THEALOZ TOTAL is well tolerated on the ocular surface.

As per the IFU, the clinical benefits of THEALOZ TOTAL are:

- THEALOZ TOTAL relieves from the symptoms of dry eyes.
- THEALOZ TOTAL soothes the eyes (from itchiness and irritation sensations).
- THEALOZ TOTAL reduces the redness of the eyes.

As per Laboratoires THEA, other clinical benefit of THEALOZ TOTAL is improvement of (global) ocular comfort.

5.2 OBJECTIVES, PRIMARY AND SECONDARY

The primary objective of the clinical investigation is to assess the performance of T2769 in contact lens wearers with dry eye symptoms in terms of dry eye symptomatology.

The secondary objective of the clinical investigation is to evaluate the performance of T2769 in terms of dry eye signs and symptoms and to evaluate the safety of T2769 in in contact lens wearers with dry eye symptoms.

5.3 SCIENTIFIC JUSTIFICATION AND CLINICAL RELEVANCE FOR EFFECT SIZES, NON-INFERIORITY MARGINS OR EQUIVALENCE LIMITS

Based on the literature (similar device clinical investigation performed in contact lens wearers using THEALOZ DUO by Fernández-Jimenez, Diz-Arias et Peral 2022), we estimate that CCI patients would be sufficient to demonstrate a clinically relevant improvement in dry eye symptoms and signs in contact lens wearers with dry eye symptoms.

5.4 PRIMARY AND SECONDARY HYPOTHESES

The hypotheses are that T2769 improves dry eye symptomatology (e.g. decrease in CLDEQ-8 score, in OSDI score, ocular discomfort assessed by VAS) and signs (e.g. increase in Schirmer and TBUT, decrease in Oxford score) at D36, in comparison to baseline.

5.5 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS

There are no specific risks and anticipated Adverse Device Effects (ADE) to be assessed during this clinical investigation.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

6.1.1 Justification of the clinical investigation design

Methodology: a prospective, single-arm, multicenter, 5-week investigation.

- Multicenter

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

- Single arm / open label design

This is a confirmatory clinical investigation to collect data on contact lens wearers with dry eye symptoms.

- Choice of the investigation population

The study population will consist of patients wearing well fitted contact lenses for a minimum of 5 days/week for 6 hours/day over at least the last month before inclusion visit and experiencing some dry eye symptoms as defined in inclusion criteria.

- Scheme of administration

The dose regimen recommended is 3 to 6 times daily. Patients can instil IMD at any time during the day, but only when wearing their contact lenses.

- Choice of the treatment period

A 5-week treatment period may allow to evaluate the therapeutic effect and to observe any potential safety issues.

A period of 1 month is usually the minimum time required to demonstrate the therapeutic effect of a product.

- Choice of primary endpoint and secondary endpoints

The primary and secondary endpoints of this clinical study have been taken into consideration based on the clinical literature review (Chalmers et al. 2016; Chalmers et al. 2012; Pucker et al. 2020; Fernández-Jimenez, Diz-Arias et Peral 2022). Consequently, these endpoints are clinically relevant, clearly defined and assessed at specified time points to provide clinical evidence on the performance and tolerance of T2769 in its intended use (i.e., improvement of the ocular signs and symptoms in DED patients).

- Symptoms assessment

Ocular symptoms as well as AEs will be assessed at all investigation visits.

The investigation flow chart is described in Table 2.

6.1.2 Description of the Measures to be Taken to Minimize or Avoid Bias

6.1.2.1 *Randomisation*

No randomisation will be performed in this clinical investigation.

6.1.2.2 *Concealment of Allocation*

Not Applicable

6.1.2.3 *Masking and Code Breaking*

Not Applicable

6.1.2.4 *Management of potential confounding factors*

Not Applicable

6.1.2.5 *Dispensing*

IMD will be dispensed by the investigator and/or pharmacist or authorised person delegated by the investigator and according to the local regulations. Each dispensing of IMDs will be recorded in the appropriate documentation.

All information regarding the usage of the IMDs will be contained in the package given to patients.

The IMDs must be dispensed only to patients in accordance with the CIP.

As soon as the patient has signed the Informed Consent, he/she will receive a patient number in the Electronic Case Report Form (e-CRF).

At the inclusion visit (Day 1), once inclusion and exclusion criteria have been checked and once the patient is eligible, he/she will be included and will be dispensed an IMD kit.

6.1.3 Primary and Secondary Endpoints, with Rationale for their Selection and Measurement

6.1.3.1 *Primary Performance Endpoint*

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

This endpoint has been chosen considering the clinical literature review (Chalmers et al. 2016; Chalmers et al. 2012; Pucker et al. 2020; Fernández-Jimenez, Diz-Arias et Peral 2022).

CLDEQ-8 is the only validated questionnaire for contact lens wearers defined in TFOS workshop on CLD.

6.1.3.2 *Secondary Performance Endpoints*

The secondary performance endpoints are:

- Change from baseline[a] (D1) in CLDEQ-8 total score* at D15.
- Soothing sensation just after (less than 5 minutes) instillation* at D15 and D36.
- Change from baseline[a] (D1) in OSDI* total score at D15 and D36.
- Change from baseline[a] (D1) in the ocular discomfort score on the VAS* at D15 and D36.
- Score of each ocular symptom throughout the day* (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation) at D15 and D36 and change from baseline[a] in the total score of these symptoms.

- Change from baseline[a] (D1) in contact lens wearing time at D15 and D36.
- Change from baseline[a] (D1) in conjunctival hyperaemia score at D15 and D36 separately in the studied eye[b] and in the contralateral eye.
- Change from baseline[a] (D1) in TBUT at D15 and D36 separately in the studied eye[b] and in the contralateral eye.
- Change from baseline[a] (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D15 and D36 separately in the studied eye[b] and in the contralateral eye.
- Change from baseline[a] (D1) in Schirmer test result (without anesthesia) at D15 and D36 separately in the studied eye[b] and in the contralateral eye.
- Performance assessment by the investigator at D15 and D36.

[a]baseline is defined as the assessment at inclusion visit before the first IMD instillation. Missing value at inclusion visit will not be replaced.

[b]defined in the statistical considerations section.

*Patient questionnaire

6.1.3.3 *Safety Endpoints*

The following safety and tolerability endpoints will be assessed:

- Treatment-Emergent Adverse Event (TEAE) by System Organ Class and Preferred Term (separately for Ocular and systemic TEAE).
- Change from baseline (D1) in Far Best Corrected Visual Acuity expressed in Log MAR at D36 separately in the studied eye and in the contralateral eye.
- Ocular tolerance assessed by the investigator at D15 and D36.
- Ocular tolerance assessed by the patient at D15 and D36.

6.1.4 Pharmacokinetics

Not Applicable

6.1.5 Biomarkers Evaluation

Not Applicable

6.1.6 Methods and Timing for Assessing, Recording, and Analysing Variables

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

Visit #1: Day 1 Inclusion visit (D1)

Visit #2: Day 15 (±1 day) (D15)

Visit #3: Day 36 (+3 days) Final visit (D36)

All visits must take place in the afternoon.

The patients will have to come to onsite visits wearing their contact lenses. After BCVA assessment, they will be removed before other ocular examination and put back again at the end of the visit. The patients will have to bring their contact lens case and cleaning solution.

The schedule of visits, including the timing of examinations and assessments is presented in Table 2 Schedule of Visits and Procedures.

6.1.6.1 *Screening Period*

Not Applicable

6.1.6.2 *Treatment Period*

Visit#1: Day 1 Inclusion visit (D1)

Visit#1 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

- Information for the patient and signature of the informed consent (can be done before this visit). See section 13.
- Demography,
- Contact lens history,
- Questioning about ocular and systemic medical and surgical history (including dry eye),
- Questioning about previous and concomitant ocular and non-ocular treatments,
- CLDEQ-8 self-questionnaire,
- OSDI self-questionnaire,
- Ocular discomfort evaluation (VAS),
- Ocular symptoms throughout the day,
- Contact lens wearing time (collected in contact lens history),
- Measurement of Far BCVA*,
- Slit lamp examination* for measuring:
    - conjunctival hyperaemia* with McMonnies photographic scale
    - TBUT*,
    - Oxford 0-15 grading scheme* (corneal and conjunctival staining by fluorescein with a yellow filter).
- Schirmer test* (without anaesthesia),
- Urine pregnancy test (if applicable) (to be done at any time during the visit),
- Verification of inclusion and exclusion criteria,
- Patient diary dispensation,
- Training of the patient for diary completion. The patient will be instructed to report the number of daily instillations in the diary, the daily lens wear duration (number of hours/day) and to bring it back at next visit,
- IMD dispensation,
- Status of the patient.

The next visit must be scheduled within 15 days (±1 day) in the afternoon. Site staff must remind the patients:

- to come at visit#2 wearing their contact lenses and bring their contact lens case and cleaning solution,
- to bring back used and unused IMD for compliance check at visit#2,
- that no IMD must be instilled during at least 2 hours before visit#2.

*Ophthalmological examinations and assessments **MUST** be performed by the **SAME** investigator.

Visit #2: Day 15 (±1 day) (D15)

Visit#2 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

- Questioning about ocular and non-ocular concomitant treatments,
- CLDEQ-8 self-questionnaire,
- Soothing sensation just after (less than 5 minutes) instillation,
- OSDI self-questionnaire,
- Ocular discomfort evaluation (VAS),
- Ocular symptoms throughout the day,
- Contact lens wearing time,
- Slit lamp examination* for measuring:
    - conjunctival hyperaemia* with McMonnies photographic scale
    - TBUT*,
    - Oxford 0-15 grading scheme* (corneal and conjunctival staining by fluorescein with a yellow filter).
- Schirmer test* (without anaesthesia),
- AE reporting,
- Device deficiencies reporting,
- Ocular tolerance assessment by the patient,
- Ocular tolerance assessment by the investigator*,
- Performance assessment by the investigator*,
- IMD Compliance / Patient diary completion review,
- Patient diary dispensation,
- Training of the patient for diary completion. The patient will be instructed to report the number of daily instillations in the diary, the daily lens wear duration (number of hours/day) and to bring it back at next visit.

The next visit must be scheduled at Day 36 (+3 days) in the afternoon. Site staff must remind the patients:

- to come at visit#3 wearing their contact lenses and bring their contact lens case and cleaning solution.
- to bring back used and unused IMD for compliance check at visit#3,
- that no IMD must be instilled during at least 2 hours before visit#3.

*Ophthalmological examinations and assessments **MUST** be performed by the **SAME** investigator.

Visit #3: Day 36 (+3 days) Final visit (D36)

Visit#3 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

- Questioning about ocular and non-ocular concomitant treatments,
- CLDEQ-8 self-questionnaire,
- Soothing sensation just after (less than 5 minutes) instillation,
- OSDI self-questionnaire,
- Ocular discomfort evaluation (VAS),

- Ocular symptoms throughout the day,
- Contact lens wearing time,
- Measurement of Far BCVA*,
- Slit lamp examination* for measuring:
    - conjunctival hyperaemia* with McMonnies photographic scale
    - TBUT*,
    - Oxford 0-15 grading scheme* (corneal and conjunctival staining by fluorescein with a yellow filter).
- Schirmer test* (without anaesthesia),
- AE reporting,
- Device deficiencies reporting,
- Urine pregnancy test (if applicable) (to be done at any time during the visit),
- Ocular tolerance assessment by the patient,
- Ocular tolerance assessment by the investigator*,
- Performance assessment by the investigator*,
- IMD Compliance / Patient diary completion review,
- Record of used and unused IMDs (in Treatment Kits Tracking Form),
- Status of the patient.

*Ophthalmological examinations and assessments **MUST** be performed by the **SAME** investigator.

6.1.6.3 *Additional/Optional Visit(s) during the clinical investigation*

Not Applicable

6.1.6.4 *Premature discontinuation Visit during the clinical investigation*

A patient who prematurely discontinues from the investigation should have, if possible, a premature discontinuation visit. This last site visit should take place as soon as possible after the patient stops taking IMD. All follow-up procedures and examinations scheduled to be performed at the final visit should be performed at the patient's premature discontinuation visit.

If the patient is tested COVID-19 positive during the study, the patient must inform the investigator. Either the patient may continue the clinical investigation when he/she can follow the CIP requirements safely and in accordance with the national/regional recommendations or the patient may be withdrawn from the clinical investigation.

Note: Included patients who withdraw will not be replaced by another patient. The patient number and associated inclusion number of the withdrawn patient must not be reassigned to a different patient.

6.1.6.5 *Additional Follow-Up Visit(s) (after the end of the treatment)*

Not Applicable

6.1.6.6 *Adaptive Follow-Up of Patients Prematurely Withdrawn due to an Exceptional Circumstance (e.g. COVID-19 pandemic)*

The benefit/risk ratio will be evaluated both by the Sponsor at global level (regulatory requirement) and by the investigator regarding the situation and local regulatory requirements in his/her country/region and in his/her own investigational site.

Either the patient may continue the clinical investigation when he/she can follow the CIP requirements safely and in accordance with the national/regional recommendations or the patient may be withdrawn from the clinical investigation.

If the patient withdrew from the clinical investigation due to an exceptional circumstance, and if an onsite visit was not authorized, a premature discontinuation visit by phone is required.

- **Premature discontinuation phone call**

- Check the IMD compliance with the patient.
- Instruct the patient to stop the IMD and keep used and unused IMD for later return.
- Ensure the continuity of artificial tears medication as per routine clinical practice.
- Collect AE/SAE and any changes in concomitant treatments.
- Collect Device Deficiency.
- Plan a safety onsite visit 4 weeks later (±7 days) and ensure that the patient understands all recommendations.
- Record the phone call and all information collected in the patient medical record.

When possible (investigator site situation evolution) and at the earliest opportunities (preferably within 4 weeks ±7 days), investigators will perform an onsite follow-up visit.

- **Safety Follow-up visit on site**

During the onsite follow-up visit after the premature discontinuation phone call, the following procedures are required:

- Ensure that dry eye is well controlled.
- Check the IMD compliance with the patient.
- Record the number of the returned used and unused IMD.
- Check that the patient had stopped the IMD and takes the new treatment, collect start and end dates of these medications.
- Collect AE/SAE and any changes in treatments.
- Record the visit and all information collected in the patient medical record.

If a safety onsite visit is still not possible, the follow-up will be done by phone or online video consultation and the patient is asked to return the used and unused investigation products later, when the situation improves or the pickup of the IMD directly from the patient will be organised. The compliance will be checked with the number of the returned used and unused IMD.

6.1.7 Equipment to be used for Assessing the Clinical Investigation Variables and Arrangements for Monitoring Maintenance and Calibration

A slit lamp will be used to measure the total ocular surface staining grade according to Oxford 0-15 grading scheme.
During the Site Qualification Visit and the Site Initiation Visit, the site must prove that he has a maintenance certificate for the slit lamp. During the clinical investigation, the monitor should verify that the maintenance is performed (cf. manufacturer guidelines).
During the clinical investigation, the same slit lamp must be used for the same patient at each visit.

6.1.8 Procedures for the Replacement of Patients

The number of included patients will be followed to obtain C evaluable patients.

Included patients who withdraw will not be replaced by another patient. The patient number and associated inclusion number of the withdrawn patient must not be reassigned to a different patient.

6.1.9 Investigation Sites

Patients will be enrolled in approximately 6 investigational sites in EU.

The Sponsor will maintain an updated list of PIs and investigation sites, separately from this CIP, throughout the duration of the clinical investigation. The definitive list will be provided with the CIR.

6.1.10 Definition of Completion of the Clinical Investigation

The clinical investigation completion is defined with the last visit of the last patient.

In the case of early termination of the clinical investigation (see Section 16.2), the date of the early termination shall be deemed to be the date of the clinical investigation completion.

6.2 IMD(s) AND COMPARATOR(S)

6.2.1 Description of the Exposure to the IMD

IMD will be administered by the patient every day for 36 + 3 days, one drop in each eye 3 to 6 times daily into the lower conjunctival sac of each eye.

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

There will be only 1 treatment group, all patients will instil T2769.

A detailed description of T2769 is available in Section 2.

6.2.2 List of any Other Medical Device or Medication to be Used during the Clinical Investigation

6.2.2.1 *Run-in Treatment/Wash-out Treatment*

Not Applicable.

6.2.2.2 *Auxiliary Products*

An auxiliary product is defined as a product used for the needs of a clinical investigation as described in the CIP, but not as an IMD.

Fluorescein Faure 0.5% unidoses: one drop will be instilled in the upper bulbar conjunctiva of each eye by the investigator at visits 1, 2 and 3 to perform the slit lamp examination: TBUT and corneal/conjunctival staining with Oxford 0-15 grading scheme. This staining is assessed with a yellow filter.

Schirmer-Plus: while the patient looks upwards, the lower lid will be drawn gently downwards and temporally. The rounded bent end of a sterile Schirmer test strip will be hooked in the lower conjunctival sac over the temporal one-third of the lower eyelid margin. After five minutes, the

moistened paper is removed and the length of the tear absorption on the strip will be measured (in millimeters).

Pregnancy test: each childbearing potential woman will perform a urine pregnancy test at Visit#1 and Visit#3.

6.2.3 Number of IMD to be Used, together with a Justification

During the clinical investigation, each patient will receive the IMD (2 vials of T2769) to cover active treatment period. One 12.5 mL ABAK® multi-dose bottle can deliver up to about 375 drops which is enough to cover 39 days treatment period taking into consideration a maximal dose regimen of 1 drop in each eye 6 times daily.

6.3 SUBJECTS/PATIENTS

6.3.1 Inclusion Criteria

Patient fulfilling all the following criteria will be eligible:

1.1. Informed consent signed and dated (obtained prior to initiating any procedures).

1.2. Patient aged ≥ 18 years old.

1.3. Well fitted contact lenses (CL) according to the investigator judgement.

1.4. Daily wearer of any type of CL for a minimum of 5 days/week for 6 hours/day over at least the last month and is willing to continue to do so during the study.

1.5. Patient with an Ocular Surface Disease Index (OSDI) score ≥ 18.

1.6. CLDEQ-8 score ≥ 12.

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6.3.2 Exclusion Criteria

Patient will NOT be eligible if ONE OR MORE of the following criteria is met:

Ophthalmic Exclusion Criteria in AT LEAST ONE EYE [2.1]

2.1.1. Far Best-Corrected Visual Acuity (BCVA) ≥+0.7 LogMar (e.g., ≤0.2 in decimal value or ≤20/100 Snellen equivalent or ≤50 ETDRS letters).

2.1.2. Severe blepharitis according to the judgment of the investigator.

2.1.3. Confirmed diagnosis of severe Meibomian gland dysfunction.

2.1.4. Presence of palpebral or nasolacrimal disorders.

2.1.5. Dry eye associated with at least one of the following diseases/symptoms:

- Ocular rosacea,
- Pterygium,
- Eyelid malposition,
- Corneal dystrophy,
- Ocular neoplasia,

- Filamentous keratitis,
- Corneal neovascularisation,
- Orbital radiotherapy,
- Cataract,
- Retinal disease.

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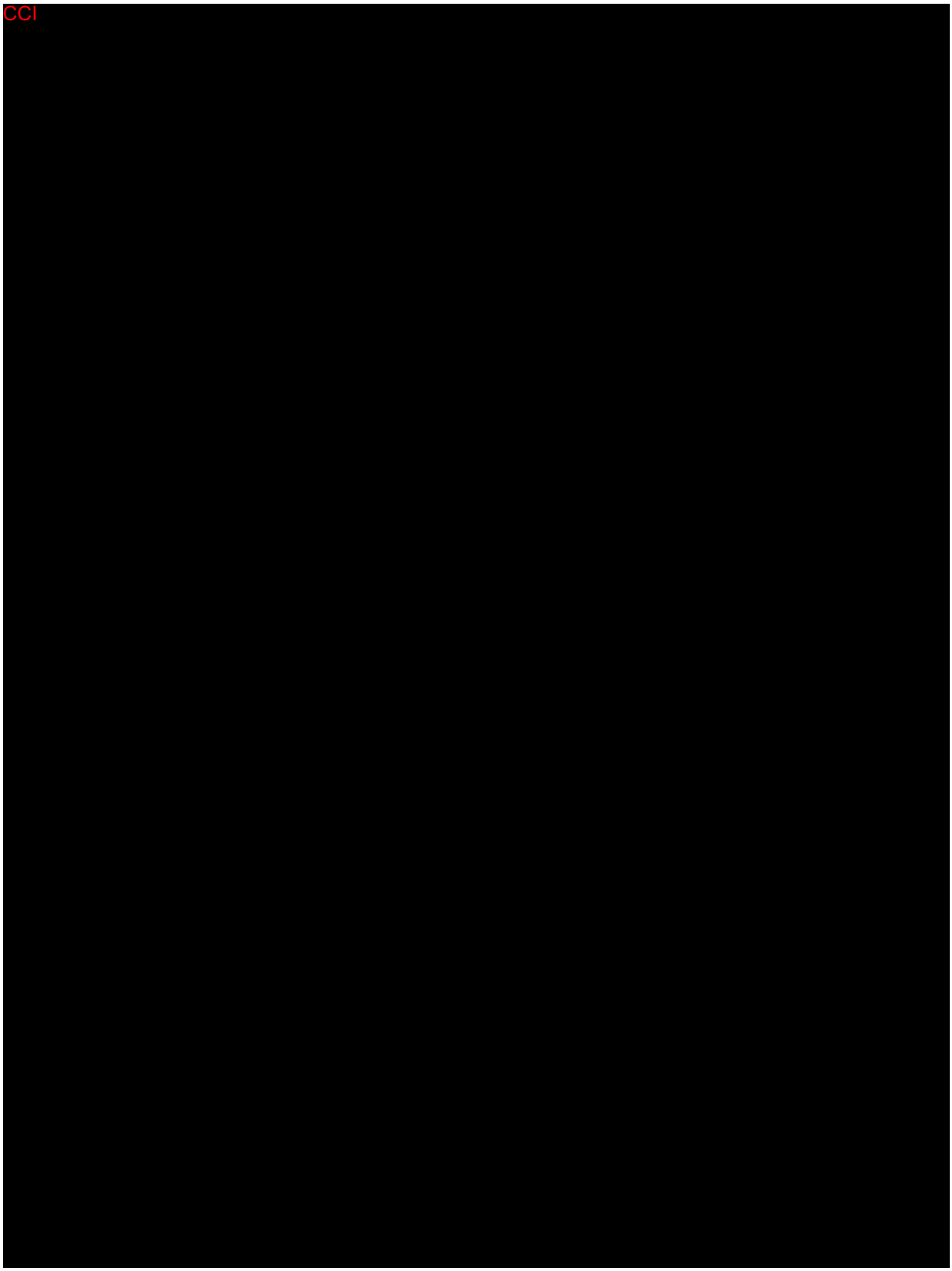

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[redacted]

6.3.3 Criteria and Procedures for Treatment/Investigation Withdrawal or Discontinuation

There are no pre-defined criteria for temporary or permanent treatment discontinuation apart from those listed below.

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

The patient must be withdrawn from the clinical investigation if, in the opinion of the investigator, there is any situation or condition which puts the patient at significant risk, especially in case of:

- Any safety reason(s)/AEs necessitating discontinuation from the investigation,
- Any abnormality with IMD,
- Lack of performance: if the patient or the investigator does not feel that the IMD has sufficiently controlled the pathology/has adequately relieved his/her symptoms,
- Patient compliance,
- Patient's request,
- Any exceptional circumstance (e.g., COVID-19 pandemic),
- Other reasons.

If a patient prematurely stops the IMD or should/wants to prematurely withdraw from the clinical investigation for any reason, the investigator (or delegated assessor) must make every effort to perform all the evaluations described for the final visit (Visit#3) as soon as possible.

The investigator (or delegated assessor if physician) will prescribe the best appropriate treatment to the patient.

In all cases, the reason(s) for withdrawal, must be recorded on the patient files (source documentation) and the primary reason, must be recorded on the e-CRF.

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 his/her general practitioner. The evidence of these contacts must be recorded in the patient files.

Screen failures are defined as patient who consent to participate in the clinical investigation and undergo visit#1 but are not subsequently included in the investigation.

If a patient is screen-failed, all reasons of screen-failure must be documented in the Source document. The screen-failed patient may be rescreened one time.

Adaptive follow-up in the case of an **exceptional circumstance (e.g. COVID-19 pandemic)** is described in section 6.1.6.6.

6.3.4 Point of Enrolment

The point of enrolment corresponds to the time at which a patient signs and dates his/her consent form. Patients are to be enrolled at about 6 investigational sites in EU.

6.3.5 Point of Randomisation

Not Applicable

6.3.6 Total Expected Duration of the Clinical Investigation

This clinical investigation is planned to start in August 2023 and to be completed in January 2024.

6.3.7 Expected Duration of each Patient's Participation

The treatment period for each patient is 36 + 3 days for a total maximum investigation duration of 39 days.

6.3.8 Number of Patients Required to be Included in the Clinical Investigation

A total of CCI patients should be included in order to have CCI evaluable patients in the FAS population.

Evaluable patients will be defined as included patients having received at least one dose of IMD.

6.3.9 Estimated Time Needed to Select this Number (*i.e.* enrolment period)

The enrolment period is estimated at about 4 months.

6.3.10 Relationship of Investigation Population to Target Population

As per IFU, the target population of the medical device is adults with dry eyes, including wearers on any type of contact lenses.

The purpose of the clinical investigation is to evaluate the safety and performance of T2769 treatment in adults, wearing any type of contact lens and who experience symptoms of dry eye and discomfort during lens wear.

Thus, the contact lens wearers population is part of the target population.

6.3.11 Information on Vulnerable, Pregnant, and Breastfeeding Population

This clinical investigation will not be conducted in vulnerable populations as children, pregnant or breastfeeding women. See Section 15.

6.4 PROCEDURES

Timing of procedures is presented in **Table 2 Schedule of Visits and Procedures**.

Some procedures must be performed by the same investigator or the same authorized assessor/delegate throughout the clinical investigation (BCVA, slit lamp examination, Schirmer test, tolerance/performance assessment by investigator).

6.4.1 Description of all the Clinical-Investigation-Related Procedures that Patients Undergo during the Clinical Investigation.

6.4.1.1 *Demographics and Screening/Inclusion Characteristics*

The following characteristics will be collected:

- Age (in years),
- Gender,
- Previous and concomitant ocular and non-ocular medications (see 6.4.1.4),
- Result of the urinary pregnancy test,
- Contact lens history:
  - contact lens type,
  - mean contact lens wearing time over the month preceding inclusion (hours/day and days/week),
  - cleaning solution type (preserved or not preserved),
  - history of contact lens intolerance.
- Ocular medical and surgical history with relevant diagnosis (including dry eye),
- Systemic medical and surgical history with relevant diagnosis.

6.4.1.2 *Performance Measures*

6.4.1.2.1 *CLDEQ-8 self-questionnaire* CCI [redacted] CCI [redacted]

The CLDEQ-8 questionnaire (Copyright© Begley & Chalmers 2016, all rights reserved) must be completed by the patient at each visit. It consists of 8 questions designed to measure dry eye symptoms specifically related to the use of contact lenses. The total score is obtained by adding the scores obtained for each answer. The final score is ranging from 1 to 37.

6.4.1.2.2 *Soothing sensation*

Patient will be asked: “How would you rate your soothing sensation just after (less than 5 minutes) study treatment instillation(s)?

The soothing sensation felt by the patient just after (less than 5 minutes) IMD instillation after 15 and 36 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 post-baseline visit.

6.4.1.2.3 *Ocular Surface Disease Index (OSDI) self-questionnaire*

The OSDI questionnaire (Schiffman et al., 2000; Miller et al., 2010) must be completed by the patient at the beginning of each visit before medical history information is collected or any investigation assessments are performed. The total OSDI score range on a scale from 0 to 100. CCI

6.4.1.2.4 *Ocular discomfort (VAS)*

Ocular discomfort (global evaluation for both eyes) will be assessed by the patient at D1, D15 and D36 visits 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.

6.4.1.2.5 *Ocular symptoms throughout the day*

CCI

6.4.1.2.6 *Daily contact lens wearing time*

CCI

6.4.1.2.7 *Slit lamp examination*

- Conjunctival hyperaemia

CCI

- Tear Break-Up Time (TBUT)

The tear film stability will be measured 3 times after the instillation of fluorescein. TBUT will be rapidly assessed and expressed in seconds. The sum of the 3 measures will also be expressed in seconds. TBUT will be measured in each eye and at each visit.

- Total ocular surface staining (Oxford scale)

The total ocular staining grade using Oxford 0-15 grading scheme will be assessed at each visit by staining in corneal area and conjunctival areas (temporal and nasal) by fluorescein with a yellow filter.

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) CCI CCI

The score for each area will be recorded for each eye. The global score (sum of score reported for each area: corneal + conjunctival) will be used for statistical analysis.

6.4.1.2.8 *Schirmer Test*

CCI

6.4.1.2.9 *Performance Assessment by the investigator*

The investigator must answer to the following question at the end of the patient examination at D15 and D36:

“Do you consider the IMD performance as:

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory”

6.4.1.3 *Safety measures*

6.4.1.3.1 *Visual acuity*

Far BCVA will be assessed in each eye at D1 and D36 using the same chart (for example a Snellen chart) throughout the clinical investigation. It can be expressed using units as /10, decimal notation, MAR, logMAR or Snellen notation. It will be analysed after conversion in LogMar. CCI [redacted]

6.4.1.3.2 *Adverse Events*

Ocular and systemic AEs will be collected by the investigator (or authorised assessor/delegate) at each visit.

In case of appearance of a new clinically significant sign or symptom, it should be reported as an AE or SAE.

In case of clinically significant worsening of a pre-existing sign or symptom, it should be reported as an AE or SAE.

The handling of AEs is detailed in Section 14.

6.4.1.3.3 *Device deficiencies*

Device deficiencies will be collected by the investigator (or authorised assessor/delegate) at each visit.

6.4.1.3.4 *Ocular Tolerance Assessment by the patient*

The investigator must ask the patient the following question in local language:

“How do you consider the study treatment ocular tolerance?

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory”

6.4.1.3.5 *Ocular Tolerance Assessment by the investigator*

The investigator must answer to the following question in local language:

“How do you consider the IMD ocular tolerance?

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory”

6.4.1.3.6 *Treatment Compliance Evaluation*

Patient will return all investigation products (IMD), whether used or unused.

For IMD *(*T2769), the patient will also have to report information about his/her compliance on a paper patient diary during the treatment period. Each day the patient will enter the date and

number of instillations* per day. Moreover, he/she will be asked to add the date and hour of last instillation before the beginning of each post-inclusion visit.

In addition, compliance will be assessed by questioning the patient during the visit (*e.g.* if there was any treatment interruption or missed instillation) and by checking the paper patient diary.

** one instillation = 1 drop in each eye*

6.4.1.4 *Prior and Concomitant Therapy*

At inclusion visits, patient will be asked what treatment he/she has taken within the last 3 months; this will be recorded on the e-CRF documenting product details, dose and treatment duration.

Concomitant treatment means any medications or non-medicinal therapies given concurrently with the IMD. Any other local or systemic treatment necessary for the patient's welfare has also to be recorded on the patient medical record and on the e-CRF documenting product details, dose and treatment duration. In case of premature discontinuation, the new treatment for dry eye with the start date and dosing must also be collected.

6.4.1.5 *Permitted Treatments*

Auxiliary products are permitted. See Section 6.2.2.

Systemic medication not listed in Table 1 Prohibited treatments (medications/non-medicinal therapies/procedures) are permitted **ONLY** if there has been no modification of the dosage in the month preceding the inclusion visit and if no modification is planned throughout the duration of the study.

6.4.1.6 *Prohibited Prior and Concomitant Medications or Treatments*

6.4.1.6.1 *Rescue Medications (RMs)*

Not Applicable.

6.4.1.6.2 *Prohibited Treatments other than Rescue Medications (RMs)*

Prohibited treatments as well as prohibited modifications during the clinical investigation are presented in the summary in the exclusion criteria and in Table 1 Prohibited treatments (medications/non-medicinal therapies/procedures).

6.4.2 Description of those Activities Performed by Sponsor Representatives (excluding monitoring)

Laboratoires THEA through Clinical Research Organisations (CROs) is responsible for selecting the investigator(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the clinical investigation.

Laboratoires THEA/representatives of Laboratoires THEA will remind the investigator upon his/her responsibilities and procedures for ensuring adequate and correct documentation.

Laboratoires THEA will inform the investigator, directly or through CRO in charge of monitoring, prior to the commencement of the clinical investigation of all relevant chemical, toxicological and clinical information required for the proper planning and conduct of the clinical investigation and will update this as often as may be necessary during the course of the clinical investigation. However, this obligation shall not require Laboratoires THEA to provide

information which is already available in published material or of which the investigator could reasonably be expected to have knowledge in view of his/her professional training.

Laboratoires THEA or CROs will nominate a suitably trained person or persons to monitor the clinical investigation and to liaise with the investigator.

Laboratoires THEA/representatives of Laboratoires THEA, will also be responsible for complying with the local regulations applicable to clinical investigation.

6.4.3 Any Known or Foreseeable Factors that may Compromise the Outcome of the Clinical Investigation or the Interpretation of Results

The population will be selected according to the inclusion and exclusion criteria to have a homogenous population.

6.4.4 Methods for Addressing these Factors in the Clinical Investigation

Not Applicable.

6.4.5 Description of the Follow-Up Period

Not Applicable

6.4.6 Appropriate Specific Medical Care Address after the Clinical Investigation

Not Applicable

6.4.7 Recommended Follow-Up Address after the Clinical Investigation

Not Applicable

6.4.8 Final Disposition or Potential Future Use of Samples obtained from Patients Address

Not Applicable

6.5 MONITORING PLAN

Monitoring arrangements and activities will be detailed in a Clinical Monitoring Plan or equivalent document.

Monitoring procedures developed by Laboratoires THÉA/CRO will be followed in order to comply with the CIP and GCP (ISO 14155 current version), and the applicable regulatory requirements. Monitoring activities will be detailed in a Clinical Monitoring plan.

On-site and checking of the e-CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. Between on-site visits, remote checking of any obvious data anomalies (data discrepancies) will be done by monitor.

The investigator(s) and site staff must be available during on-site monitoring visits for:

- medical questions concerning patient's safety,
- verification of data from source documentation,
- possible e-CRF corrections and queries resolution,
- IMDs/non IMDs questions.

In the case of an exceptional circumstance (*e.g.* COVID-19 pandemic), the modalities of monitoring activities may be adapted to the situation, to ensure the safety of the patients, monitors, and site staff, based on a risk-based approach. The Clinical Monitoring Plan or equivalent document will be updated accordingly.

6.5.1 Source Documents

Each participating investigational site will maintain appropriate medical and research records in compliance with GCP (ISO 14155 current version) and any other regulatory and institutional requirements for the protection of patient's confidentiality.

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

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

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

All following patient's assessments will be collected via a paper diary and/or paper questionnaire and will be considered as source data:

- IMD compliance: number of instillations/day,
- Contact lens wearing time,
- VAS,
- OSDI questionnaire,
- CLDEQ-8 questionnaire.

The following information should be entered into the patient's medical record:

- Patient's name, date of birth, gender,
- Patient's contact information,
- The date the patient entered the study and patient's number,
- The clinical investigation title and/or the clinical investigation number,
- A statement that informed consent was obtained (including the date) and patient's card was provided to the patient; data protection consent or other country and local patient privacy required documentation for this investigation have been obtained (including the date),

- Date of all patient's visits,
- Investigated disease history:
    - Diagnosis of DED for each eye,
    - Date of onset of the diagnosis in each eye (at least months/year),
    - Previous use of artificial tears,
    - Contact lens history (type of lens, wearing time during at least the last month per week and day, type of cleaning solution (preserved or not), any history of contact lens intolerance, any other important information regarding contact lens),
- Ocular and systemic medical and surgery history with diagnosis dates (including dry eye),

For systemic medical history, the information could be collected via patient interview. For ophthalmic medical history of referred patient's, a letter from the referring ophthalmologist is strongly recommended.

- Prior and concomitant medications (list all prescription and non-prescription medications being taken at the time of enrolment and within 3 months before inclusion visit. At each subsequent visit, changes to the list of medications should be recorded),
- Name/initials and signature of the persons who perform assessments,
- Visual acuity values (standard BCVA value with used chart name),
- Slit-lamp examination results with score of ocular signs, conjunctival hyperaemia, corneal and conjunctival fluorescein staining, TBUT,
- Schirmer test results for both eyes,
- Occurrence and status of any AEs,
- Occurrence and status of any DD,
- Review of inclusion/exclusion criteria and patient's status (confirmation of patient eligibility or not, reason for screen failure if applicable),
- Ocular tolerance and performance assessment by Investigator,
- Information on diary dispensation to the patient and instructions correctly provided,
- Information on IMD dispensation, including kit number assignment,
- IMD compliance collected by reviewing patient's diary and interview and checked against returned IMD,
- Information on used/unused IMD by patient,
- The date of the patient exited the study and a notation as to whether the patient completed the study or reason for discontinuation.

6.5.2 Source Data Verification

One of the primary responsibilities of monitoring is the Source Data Review (SDR) to check quality of source, review CIP compliance, ensure the critical processes and source documentation are adequate, to ascertain Investigator involvement and appropriate delegation and assess compliance to other areas (e;g; SOPs, GCP, ISO 14155 current version). This will

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

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

Source Data Verification (SDV) will be recorded in e-CRF and SAE/pregnancy related documents, consisting in a comparison of the source documentation and other records relevant to the investigation.

The SDV will ensure the data are Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available (ALCOACCEA guiding principles).

Source Data Monitoring combines:

- ✓ Site Monitor review of the source data for a patient in order to confirm that the site is compliant with ICH GCP, ISO 14155 current version and the CIP,
- ✓ Evaluation of the conformity of the data presented in CRF, or other Sponsor-provided documents, with the available Source Data.

SDR can be done alone, but SDV cannot be done without prior SDR, since validating data transcription is not useful if CIP and GCP compliance have not been confirmed first.

6.5.3 Case Report Forms

The patients will be monitored throughout the investigation and all results of evaluations will be recorded in an e-CRF.

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

The investigator and authorised delegate(s) will have secured access to enter the data in the appropriate sections of the e-CRF.

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

The investigator is required to prepare and maintain adequate and accurate ocular and systemic history designed to record all observations and other data pertinent to the investigation for each patient.

The investigator is responsible for ensuring that data are properly recorded on each patient's e-CRF and related documents.

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

The investigator should personally electronically validate and sign e-CRFs to ensure that the observations and findings are recorded on the e-CRF correctly and completely.

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

A copy of completed CRFs pages, SAE / Pregnancy will be stored in the investigator's archives for at least 10 years after the clinical investigation with the device in question has ended, or, in

the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

7 STATISTICAL DESIGN AND ANALYSIS

The Statistical Analysis Plan (SAP) will provide, before locking the database detailed methods for the analyses outlined below.

Any changes from the planned analyses will be described and justified in the final CIR.

7.1 ANALYSIS POPULATION AND PROCEDURES

The following analysis sets will be considered:

- **Safety set:**

All enrolled patients, having received at least one instillation of IMD.

The safety set will be the primary population for safety analysis.

- **Full-Analysis Set (FAS):**

All enrolled patients having received at least one instillation of IMD.

The FAS will be the primary population for performance analysis.

- **Per protocol (PP) set:**

Subset of the FAS including patients without any major CIP violations likely to seriously affect the primary outcome of the study.

Deviations from the CIP will be defined and assessed as “minor” or “major” in cooperation with the sponsor during a data review meeting before the database lock.

The PP set will be considered as secondary population and will be used for sensitivity analyses of the primary and secondary endpoints.

7.2 STATISTICAL ANALYSIS

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

Qualitative variables (Categorical data) will be summarized in summary tables indicating the number of non-missing observations (n), count and percentage of each modality, and 95% CI.

Baseline is defined as the assessment at D1 visit before the first IMD. Missing value at inclusion visit will not be replaced.

For endpoints defined as change from baseline (D1), the descriptive statistic by visit and the change from baseline will be presented.

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

CCI

[redacted]

CCI

Disposition, demographics, baseline characteristics including contact lens history, medical/surgical history, previous and concomitant treatments, and exposure will be summarized for the FAS and PP.

7.2.1 Performance Analyses

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

The detailed analysis methods for primary and each secondary performance variables will be discussed further in the SAP.

Primary performance endpoint

The primary performance endpoint is the change from baseline (D1) to D36 in the CLDEQ-8 total score. Estimate of the change and associated 95% confidence interval will be provided, as well as p-value for the paired t-test. Analysis will be performed on observed cased (without imputation).

Sensitivity analysis of the primary performance endpoint

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

Secondary performance endpoints

The secondary performance endpoints are:

- Change from baseline in CLDEQ-8 total score at D15.
- Soothing sensation at D15 and D36.
- Change from baseline in OSDI total score at D15 and D36.
- Change from baseline in the ocular discomfort score on the VAS at D15 and D36.
- Score of each ocular symptom throughout the day (burning/irritation, stinging/eye pain, itching/pruritus, eye dryness feeling, tearing, foreign body sensation) at D15 and D36 and change from baseline in the total score of these symptoms.
- Change from baseline in contact lens wearing time at D15 and D36.
- Change from baseline in conjunctival hyperaemia score at D15 and D36 separately in the studied eye and in the contralateral eye.
- Change from baseline in TBUT at D15 and D36 separately in the studied eye and in the contralateral eye.
- Change from baseline in total ocular surface staining grade according to Oxford 0-15 grading scheme at D15 and D36 separately in the studied eye and in the contralateral eye.

- Change from baseline in Schirmer test result (without anesthesia) at D15 and D36 separately in the studied eye and in the contralateral eye.
- Performance assessment by the investigator at D15 and D36.

For quantitative variables, data will be first presented descriptively. Change from baseline values will be analyzed using the paired t-test in the same way as for the primary endpoint. Non-parametric test (i.e. Wilcoxon Signed Rank Test) will be performed in case of non-normality.

Qualitative variables will be presented descriptively. In addition, for each ocular symptom throughout the day, as well as for conjunctival hyperaemia, summaries will be also presented in classes: improvement (e.g. decrease from baseline), stable, worsening.

Analysis will be performed on observed cased (without imputation). The analysis of the secondary performance endpoints will be repeated on the PP.

7.2.2 Safety Analyses

Safety endpoint will be analysed in the Safety set.

Ocular and systemic adverse events (AEs)

Ocular and systemic AE reported during the investigation will be coded using the Medical Dictionary for Regulatory Activities (MedDRA dictionary).

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

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

TEAEs are AEs that occurred after the first IMD instillation. AEs that occurred the day of the first IMD instillation will be reviewed during a data review meeting to decide if they have to be considered as TEAE or not.

Separate descriptions of ocular and systemic TEAEs will be performed as below:

- Number and percentage of patients experiencing at least one AE, SAE, IMD-related AE, and AE leading to premature investigation IMD discontinuation.
- Number and percentage of patients experiencing at least one AE, as well as the number of AEs, by SOC and Preferred Term (PT). The same summary table will be performed for SAEs, IMD-related AEs, IMD-related SAEs and AEs leading to premature investigation IMD discontinuation.
- Number and percentage of patients with IMD-related AEs, by SOC, PT and severity.

Documented list of individual data concerning TEAEs will be performed. Individual patient data listings of TEAEs will be performed for overall AEs, SAEs and IMD-related SAEs, separately for ocular and systemic AEs.

Far best-corrected visual acuity (in logMAR) and tolerance assessments by the investigator and by the patient will be analysed descriptively. Device deficiencies will only be listed.

Other safety analysis will be detailed in the SAP.

7.3 ANALYTICAL PROCEDURES

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

Qualitative variables (Categorical data) will be summarized in summary tables indicating the number of non-missing observations (n), count and percentage of each modality, and 95% CI.

7.4 SIGNIFICANCE LEVEL AND THE POWER OF PRIMARY ENDPOINT(S) AND THE OVERALL STATISTICAL TESTING STRATEGY

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

The paired comparison between visits data will be performed at a two-sided significance level of 5%.

7.5 SAMPLE SIZE CALCULATION AND JUSTIFICATION

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

A total of CCI patients should be enrolled in the study to take into account approximately 10% of non-evaluable patients.

7.6 RATIONALE FOR THE NUMBER OF PROCEDURES TO BE PERFORMED BY A SINGLE USER AS PART OF THE LEARNING CURVE AND HOW THESE DATA ARE TO BE ANALYSED

Not Applicable.

7.7 PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE CLINICAL INVESTIGATION

Clinically significant reduction of dry eye symptoms and favorable safety profile.

7.8 INTERIM ANALYSIS, CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

No Interim Analysis is planned.

7.9 MANAGEMENT OF BIAS AND, WHEN RANDOMISATION, MATCHING OR BLINDING ARE APPLIED, PLAN FOR ASSESSMENT OF SUCCESS THEREOF.

Not Applicable.

7.10 MANAGEMENT OF POTENTIAL CONFOUNDING FACTORS

Not Applicable.

7.11 DESCRIPTION OF PROCEDURES FOR MULTIPLICITY CONTROL AND ADJUSTMENT OF ERROR PROBABILITIES

Not Applicable.

7.12 SPECIFICATION OF SUBGROUPS

Not Applicable.

7.13 MANAGEMENT, JUSTIFICATION, AND DOCUMENTATION OF MISSING, UNUSED OR SPURIOUS DATA, INCLUDING DROP-OUTS

Performance and safety analysis will be analysed on data as observed.

7.14 EXPLORATORY AND SENSITIVITY ANALYSIS

The analysis of the primary and secondary performance endpoints will be repeated on the PP.

7.15 PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any changes from the planned analyses will be described and justified in the SAP and the final clinical investigation report.

7.16 STRATEGY FOR HANDLING THE POTENTIAL IMBALANCE OF THE NUMBERS OF SUBJECT/PATIENT ACROSS INVESTIGATION SITES (FOR MULTICENTRE INVESTIGATION)

The clinical investigation will be conducted in compliance with the CIP in all investigation sites involved in the clinical investigation.

Study team training is planned prior to the commencement of the study. Procedures will be standardized across study centres as much as is feasible.

7.17 DEFINE A STRATEGY FOR POOLING DATA, IF APPLICABLE.

Not Applicable.

8 DATA MANAGEMENT

8.1 METHODS FOR DATA ENTRY AND COLLECTION

Each participating site will maintain appropriate medical and research records for this investigation in compliance with GCP - ISO 14155:2020 sections 3.47, 4.48 and 7.8.1 and any other regulatory and institutional requirements for the protection of patient's confidentiality.

8.2 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING, AND ISSUING AND RESOLVING DATA QUERIES

The investigator will ensure that his/her centre has the necessary facilities, time and staff for the conduct of the investigation, and that these will be maintained for the duration of the investigation.

The investigator and authorised delegate(s) will ensure that proper data for the clinical investigation are collected and accurately documented in the appropriate sections of e-CRFs.

The investigator will cooperate with Laboratoires THÉA and any person nominated by Laboratoires THÉA to monitor or supervise the conduct of the investigation.

8.3 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS

Entries in e-CRF shall be made complete, correct and in a timely manner.

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

Data Management activities will be performed by Laboratoires THÉA Data Manager and/or the CRO in charge of Data Management and will be defined in the Data Management Plan (DMP).

Diagnosis for AEs and medical history will be coded using MedDRA. Whodrug Anatomic Therapeutic Chemical (ATC) code will be used for previous and concomitant treatment coding. Versioning will be specified in the DMP.

8.4 PROCEDURES TO MAINTAIN AND PROTECT PATIENT PRIVACY

Laboratoires THÉA, as Sponsor of the investigation, acting as data controller and is committed to protecting the privacy and security of personal data processed for the purposes of the clinical investigation under the conditions define below:

- **Compliance with the General Data Protection Regulation (GDPR) and other applicable law or regulation:**

Laboratoires THÉA is committed to comply with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (hereinafter the "GDPR") and any other applicable law or regulation related to the protection of personal data.

It is specified that for the clinical investigation, Laboratoires THÉA also comply with the applicable guidelines of the French supervisory authority ("Commission Nationale de l'Informatique et des Libertés" hereinafter the "CNIL") as defined in the deliberation n°2019-153 of 3 May 2019 of the CNIL, also called the "MR-001".

- **Data subjects information on the processing of their personal data**

The data subjects namely the patients and the investigator, including the personnel working with the investigator, are informed of the collection and processing of their personal data for the realisation of the clinical investigation.

In particular, the patients are informed by the investigator during the delivery of the Informed Consent Form (ICF) where all the mandatory information of article 13 of the GDPR are provided.

- **Data subjects exercise of their rights on their data**

The data subjects, namely the patients and the investigator, including the personnel working with the investigator, have the right, under the conditions and within the limits provided by the regulations, to access, rectify, delete or determine guidelines as to the use of their personal data after their death, as well as the right to oppose or request the limitation of processing.

In addition, and according with article L1111-7 of the French Public Health Code, the patients can access to their personal data by asking to the investigator.

For all requests concerning the rights of the patients regarding their personal data, they are advised to contact the investigator who will in turn contact Laboratoires THÉA. Otherwise, Laboratoires THÉA named a Data Protection Officer who can be contacted by the patients.

The data subjects, namely the patients and the investigator, including the personnel working with the investigator, have the right to bring a complaint with the supervisory authority, namely the CNIL in France and/or local equivalent of CNIL.

8.5 METHODS FOR DATABASE LOCKING AT THE START OF THE ANALYSIS AND STORAGE UPON COMPLETION OF THE CLINICAL INVESTIGATION

The database lock consists in the removal or changing of user access for database to prevent any further changes to the data. The database lock enables data collected to be used for formal analysis or submission to a regulatory authority. Database lock occurs following the conduct of the study.

Database will be locked when all data will be entered and clean. Data Management CRO coordinates the activities around Database Lock, including completing the Database Lock Checklist, managing Database Lock Form, and ensuring archival activities are complete.

8.6 CONFIDENTIALITY

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the IMD, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The investigator will agree to use the information only for the purposes of carrying out this clinical investigation and for no other purpose unless prior written permission from the Sponsor is obtained.

Laboratoires THÉA has full ownership of the original e-CRFs completed as part of the clinical investigation.

8.7 DATA RETENTION PROCEDURES AND SPECIFIED RETENTION PRIOD

The investigator must retain the patient identification codes for at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market, to meet the Sponsor local regulatory requirements. The investigator must produce investigation documentation or supply copies thereof to Sponsor, its designee or to CAs upon request, while ensuring patient confidentiality at all times.

8.8 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE

8.8.1 Monitoring/Data Audits

Laboratoires THÉA/representatives of Laboratoires THÉA shall be permitted to inspect any proposed investigational site prior to commencement and during the course of the clinical investigation to ensure that the investigational site is suitable and has the suitable facilities, staff and capacity for the conduct of the clinical investigation.

The e-CRFs should be available for review by the clinical monitor or auditor or national regulatory inspectors. The investigator is required to give access to all source documents and investigation data. Laboratoires THÉA and CROs will not require the investigator or any member of their staff to take any action or be a party to any action which is contrary to the laws of the country in which the clinical investigation is being carried out or to medical ethics.

8.8.2 On-site Audits/Regulatory Inspection

CAs, Independent Ethics Committees/ Institutional Review Boards (IECs/IRBs), and/or Laboratoires THÉA's Clinical Quality Assurance Group may carry out on-site audits and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the Sponsor of the necessary support at all times.

The clinical investigation may be subjected to auditing by representatives of the Sponsor and/or to inspection(s) by authorized representatives of local and/or foreign CAs. In case of an audit or inspection, the investigator will be informed in advance.

9 APPROVAL OF THE CLINICAL INVESTIGATION AND AMENDMENTS

Prior to starting the clinical investigation, the CIP and other relevant documents will be submitted and approved by the IEC/IRB and/or CAs, in accordance with regional/local regulatory requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the investigation.

Full compliance with this CIP must be sought. To alter the CIP, amendments must be written, approved by the appropriate personnel, and by IEC/IRB/CAs prior to implementation.

All amendments will be distributed to all CIP recipients, with appropriate instructions.

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

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

The Sponsor will promptly report the following for review or information to the Ethics Committee(s) and the CA for:

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

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

10 DEVIATIONS FROM CIP

The investigator will conduct the clinical investigation in accordance with this CIP, all relevant local laws, regulations or guidelines and in accordance with the principles of GCP – ISO 14155 current version. The investigator should not initiate the clinical investigation before:

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

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

At the end of the clinical investigation, CIP deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of patients from the analysis sets (see details of analysis sets in section 7.) will be discussed during the data review meeting.

11 IMD ACCOUNTABILITY

11.1 DESCRIPTION OF THE PROCEDURES FOR THE ACCOUNTABILITY OF IMD

Patients will return used and unused IMDs to the site at each visit.

The investigator or accredited/authorized person delegated by the investigator and according to the local regulations or pharmacist counts the number of IMDs remaining in the returned pack, completes and validates the "Treatment Tracking Form" (used, not used, not returned IMD).

All IMDs will be retained for inspection by the study monitor. The monitor will, upon completion of drug count and validation of the return section of the "Treatment Tracking Form", collect used/unused/broken containers of the supplied investigational products and these will be returned as instructed by Laboratoires THÉA.

11.2 PROCEDURES AND PARTICULAR MATERIALS AND INSTRUCTIONS FOR THE SAFE RETURN OF IMD, INCLUDING THOSE THAT ARE POTENTIALLY HAZARDOUS

The IMD used and unused will be returned to the depot in France for destruction.

This return will be prepared by the site team with the help of Monitor. The return request will be sent to the CRO of packaging/labelling. At receipt, the packaging and labelling CRO must confirm the good receipt to the site team and monitor.

The return will be stored in the depot in waiting the authorization of destruction by the sponsor.

12 STATEMENTS OF COMPLIANCE

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

Prior to commencement of the clinical investigation, the Sponsor or his legal representative in the community must submit a valid application, with the same version of the documentation, to the IEC and the CA (see Section 9).

Before the investigation starts, the clinical monitor must ensure that all relevant documents are available and that IEC/IRB/CAs authorisation(s) and approval(s) have been obtained. Only then, arrangements for shipment of the clinical supplies can be made and start of recruitment can begin.

The Sponsor or his legal representative will report any amendments (see Section 9) and safety-related events (see Sections 14.5 and 14.6) according to the local regulations.

The Sponsor will notify each IEC/IRB/CAs concerned of the end of a clinical investigation in all countries in which the clinical investigation has been conducted. That notification will be made within 90 days from the end of the clinical investigation in the last country in which the clinical investigation has been conducted/in accordance with the local regulations.

If the clinical investigation has terminated prematurely, the reason for the termination must be given (see Section 16.2)

When a temporarily halted clinical investigation is resumed the Sponsor will inform all involved investigators and must notify IEC/IRB/CA concerned through the EU portal and/or another way within 15 days from the restart of the temporarily halted clinical investigation in all country concerned.

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him/her and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this clinical investigation are governed by the applicable law.

The Sponsor will arrange for patients participating in this clinical investigation to be insured against financial loss due to personal injury caused by the products being tested or by medical steps taken in the course of the clinical investigation.

When required, a hospital specific indemnity agreement and/or an investigator specific agreement will be used.

13 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s) and adhere to the International Standards ISO 14155 on GCP for medical devices and the requirements in the Declaration of Helsinki – October 2013.

Prior to any investigation-related activity or any discontinuation of current medication, the investigator must give the patient (or the patient's legally authorized representative) oral and written information about the aims, methods, anticipated benefits, potential risks and inconveniences of the clinical investigation. The measures taken to safeguard the patient's privacy and the protection of personnel data should also be described in the informed consent. The patients must be informed about their right to abstain from participating in the clinical investigation and to withdraw their consent at any time without affecting their medical care.

Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the clinical investigation and to decide whether or not to participate in the clinical investigation. All questions about the clinical investigation 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 his/her informed consent.

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

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

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

As soon as the patient has signed the Informed Consent, he/she will receive a patient number.

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

14 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 DEFINITION OF ADVERSE EVENT (AE) AND ADVERSE DEVICE EFFECT (ADE)

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

NOTE:

- This definition includes events related to the IMD or the comparator
- This definition includes events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the use of the IMD or comparator.

Adverse device effect (ADE) is an AE **related** to the use of an IMD.

NOTE:

- This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction* of the IMD;
- This definition includes any event resulting from use error or from intentional misuse of the IMD.
- This includes comparator if the comparator is a medical device.

*Malfunction is defined as a failure of an IMD to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

Treatment-emergent AE (TEAE): AE that occurs or that worsens in severity after at least one dose of IMD has been administered/applied.

14.2 DEFINITION OF DEVICE DEFICIENCIES

Device Deficiency (DD): Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE:

- DD include malfunctions, use errors, and inadequate labelling.
- This definition includes DD related to the investigational medical device or the comparator.

14.3 DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) OR SERIOUS ADVERSE DEVICE EFFECT (SADE) AND UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS

A **Serious Adverse Event (SAE)** is an AE that:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in

- ✓ A life-threatening illness or injury, or
- ✓ A permanent impairment of a body structure or a body function, or
- ✓ In-patient or prolonged hospitalization, or
- ✓ Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or
- ✓ Chronic disease

- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

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

Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) is a SADE which by its nature, incidence, severity or outcome has not been identified in the current in the current risk assessment.

NOTE: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

14.3.1 Definition of the Severity of an Adverse Event

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

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

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

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

Caution: The term "severe" is used to describe the intensity (severity) of the event. This means it is not the same as "serious" used to describe the seriousness of SAE which is based on patient event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (see section 14.3 for having the definition of a SAE).

14.3.2 Causality Relatedness to the IMD

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

Each AE will be classified according to five different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational device or the investigation procedures.

1. Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the device or investigation procedures;
- the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedures;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

2. Possible: The relationship with the use of the investigational device or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

The sponsor and the investigators will distinguish between the adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device.

Complications caused by concomitant treatments, not imposed by the clinical investigation plan, are considered not related. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the adverse event, the sponsor should not exclude the relatedness; the event should be classified as "possible" and the reporting is not delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

14.4 RECORDING AES

AEs recording and reporting will extend from signing of informed consent until the final visit. If the investigator is aware of an AE occurring within one month after final investigation visit and that he/she considers there is a causal relationship with the IMD, the AE should be recorded in the e-CRF.

The investigator shall:

a) Record all AEs, regardless of the relationship to IMD, in the e-CRF, together with an assessment.

b) Report to the Sponsor, without unjustified delay, all serious AEs; this information shall be promptly followed by detailed written reports.

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

All AE reports should contain: a brief description of the event (diagnosis, localisation …), date and time of onset (if needed), duration (hours or days), intensity of symptoms (severity), treatment required, relationship with IMD and CIP procedure, action taken with the IMD, outcome, date and time of resolution and whether the event is classified as serious.

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

14.5 REPORTING OF SAE

Reporting by the investigator to the Sponsor

In case of SAE, the investigator must:

Complete the relevant e-CRF pages and the SAE form with all available initial information **within 24 hours of being aware of it.**

A SAE paper form CCI [redacted] will have to be completed, dated and signed by the investigator and send by email to: trialsafety@theapharma.com or by fax to: +33 4 73 98 14 24.

The initial report must be as accurate as possible, including details of the current illness, an assessment of the causal relationship between the event and the IMD. Additional follow-up reports must be sent back to Laboratoires THÉA within 24 hours upon receipt of follow-up information query.

In addition, the following information have to be recorded in the appropriate sections of the e-CRF:

- Demography,
- Medical and surgical history,
- Previous and concomitant medication,
- Investigational medication administration record.

The investigator is responsible for ensuring the follow-up of any patient who experiences a SAE during the clinical investigation. The investigator or an appropriate qualified physician must re-examine the patient at regular intervals until completion of the Last Patient Last Visit. Further follow up information will be reported to Laboratoires THÉA.

If the investigator is aware about any SAE occurring **within 1 month after the final visit** and that he/she considers that it is related to the IMD, and therefore deemed as a possible SADE, the investigator must report the SAE to the Sponsor immediately.

As for all other investigational documents, the investigator will retain a copy of the SAE form as per regulatory requirements for at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

Reporting by the Laboratoires THÉA through CRO to Competent Authorities/Ethics Committees

Laboratoires THÉA must report to the National CAs where the clinical investigation has commenced:

- a SAE **that has a causal relationship with the investigational device**, which indicates an imminent risk of death, serious injury, or serious illness and hat requires prompt remedial action for other patients, users or other persons or a new finding to it: immediately, **but not later than 2 calendar days after**,

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

- any other SAE **that has a causal relationship with the investigational device**: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

After consultation with Laboratoires THÉA, the investigator may be required to provide information about certain SAE to the IEC according to the institutional policy.

14.6 REPORTING OF DEVICE DEFICIENCIES

If the investigator observes any abnormality and/or deficiency of T2769, the investigator must report to Laboratoires THÉA **within 24 hours of being aware of it** CCI [redacted] CCI [redacted]

Laboratoires THÉA must:

- review all Device Deficiencies (DD), determine and document in writing whether they could have led to a SADE; in case of disagreement between the sponsor and the PI(s), the sponsor shall communicate both opinions to concerned parties

- report to regulatory authorities/IEC/investigators, within the required time period, **any device deficiencies that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.**

Once Laboratoires THÉA is made aware of any deficiency with any components of the IMD and in function of the type of deficiency, Laboratoires THÉA will take the appropriate decision to maintain the security/safety of patients.

14.7 FOLLOW-UP OF PATIENT AFTER AE

The investigator is responsible for ensuring the follow-up of any patient who experiences an AE during the investigation.

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.

In case of SAE, the investigator or an appropriate qualified physician must re-examine the patient at regular intervals until the event has resolved or stabilised at a level acceptable to the investigator and Medical expert and/or until completion of the "Last Patient Last Visit".

Further follow up information will be reported to Laboratoires THÉA.

14.8 MANAGEMENT OF PREGNANCY

In case of the investigator or an appropriate qualified physician is informed that a patient becomes pregnant while taking IMDs, she will be immediately withdrawn from the clinical investigation and she will be followed until the outcome of the birth is available.

A communication will be sent by the investigator to Laboratoires THÉA as soon as he/she has knowledge of the normal outcome. Conversely, if the outcome of the pregnancy meets the criteria of SAE (*e.g* spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital abnormality, birth defect), the investigator should follow the procedure for reporting of SAEs.

Handling of a pregnancy occurring throughout the investigation follows the same reporting procedure as per an SAE notification.

Upon medically confirmed pregnancy during the clinical investigation the investigator must:

- Report immediately (maximum 24 hours) the pregnancy status to Laboratoires THÉA using the email **trialsafety@theapharma.com**
- Discontinue the IMD

- Perform / ensure assessment until delivery of a thorough investigation of the fetus
- Remain responsible for any medical advice he/she might sought thus making appropriate decision upon pregnancy
  Report to Laboratoires THÉA Follow-Up data / update(s) using the SAE form.

14.9 LIST OF FORESEEABLE AES AND ANTICIPATED ADVERSE DEVICE EFFECTS, TOGETHER WITH THEIR LIKELY INCIDENCE, MITIGATION OR TREATMENT

According to the IMD leaflets, the following side effects are known: rare possibility of mild eye irritation and ocular redness.

When you use eye drops, you might experience disturbing symptoms such as burning sensation, stinging sensation, foreign body sensation in the eye and blurred vision for a short time.

14.10 LIST OF NON-REPORTABLE ADVERSE EVENTS

Not Applicable.

14.11 INFORMATION REGARDING THE IDMC

Not Applicable.

15 VULNERABLE POPULATION

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

If the patient is not capable of giving consent, the written consent of the patient’s legal representative will be required before participation in the clinical investigation (see section 13).

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 TEMPORARY HALT OF THE INVESTIGATION

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

As required by the Clinical Trials legislation, in the case of temporary halt of the clinical investigation:

- For reasons not affecting the benefit-risk balance, the Sponsor shall notify each country concerned through the EU portal within 15 days from the temporary halt of the clinical investigation.
- For reasons of a change of the benefit-risk balance the Sponsor shall notify without undue delay but not later than in 15 days of the date of the temporary halt in each country concerned through the EU portal of the reasons for such action and, follow-up measures for the patients.
- For an exceptional circumstance (e.g. COVID-19 pandemic), the Sponsor will follow the CAs' recommendations.

When a temporarily halted clinical investigation is resumed the Sponsor will inform all involved investigators. The Sponsor must notify IEC/IRB/CA concerned through the EU portal with the reason(s) for the suspension, as per the applicable regulatory requirement(s).

That notification will be made within 15 days from the restart of the temporarily halted clinical investigation in all country concerned.

If a temporarily halted clinical investigation is not resumed within two years, the expiry date of this period or the date of the decision of the sponsor not to resume the clinical investigation, whichever is earlier, shall be deemed to be the date of the end of the clinical investigation.

The restart of the clinical investigation following a temporary halt shall be deemed to be a substantial modification.

16.2 EARLY TERMINATION OF THE INVESTIGATION

The Sponsor or the investigator has the right to terminate the clinical investigation for any safety, ethical or administrative reason at any time. As far as possible, this should occur after mutual consultation.

As required by the Clinical Trials legislation, in the case of early termination of the clinical investigation:

- For reasons not affecting the benefit-risk balance, the Sponsor shall notify each country concerned through the EU portal of the reasons for such action and, when appropriate, follow-up measures for the patients.
- For reasons of a change of the benefit-risk balance the Sponsor shall notify without undue delay but not later than in 15 days of the date of early termination in each country concerned through the EU portal of the reasons for such action and, follow-up measures for the patients.

The investigator, IEC or CA may prematurely terminate participation at the investigational sites for which they are responsible.

Should the clinical investigation be terminated prematurely, all investigational materials (IMDs, completed, partially completed, etc.) must be returned to the Sponsor or the Sponsor's representative as if the clinical investigation had been completed.

Laboratoires THÉA shall have the right to terminate the clinical investigation at any time on written notice to the investigator. Without in any way limiting this right, Laboratoires THÉA would normally only terminate the clinical investigation in the following circumstances:

- Occurrence of
    - new events related to the conduct of an investigation or the development of an IMD likely to affect the safety of patients, such as:
        - a SAE which could be associated with the investigation procedures and which could modify the conduct of the clinical investigation,
        - a significant hazard to the patient population such as lack of performance of an IMD used for the treatment of a life-threatening disease,
        - a major safety finding from a newly completed animal study/investigation (such as carcinogenicity),
    - a temporary halt of an investigation for safety reasons if the clinical investigation is conducted with the same IMDs in another country by the same Sponsor.
- If severe and/or serious AEs with the IMD in human or animal studies should indicate discontinuation of the clinical investigation.
- If Laboratoires THÉA should wish to discontinue the clinical investigation for commercial reasons.
- If Laboratoires THÉA had reasons to believe that the clinical investigation could not be satisfactorily completed, including, but not limited to, the reason that inadequate numbers of patients could be enrolled or insufficient investigational sites found within the necessary time.

In the case of early termination of the clinical investigation, the date of the early termination shall be deemed to be the date of the end of the clinical investigation.

16.3 REQUIREMENTS FOR PATIENT FOLLOW-UP AND CONTINUED CARE

In the case of temporary halt or early termination of the clinical investigation, the requirements for patient follow-up will depend on the circumstance of the temporary halt or early termination:

- For reasons not affecting the benefit-risk balance, according to the Sponsor recommendations, the investigator could decide if the patient may continue the clinical investigation as planned or if the patient should be withdrawn from the clinical investigation.
- For reasons of a change of the benefit-risk balance, the patient should be withdrawn from the investigation and the IMD must be discontinued.
- For an exceptional reason (e.g. COVID-19 pandemic), each investigator has to decide whether the patient continued the clinical investigation when able to follow the CIP requirements safely or to withdraw the patient from the investigation, based on his/her assessment of the benefit/risk ratio regarding the COVID-19 pandemic situation in his/her country/region and own investigational site, in accordance with the national/regional recommendations.

This concerns all patients still on-going in the clinical investigation at the time of temporary halt or early termination.

If a patient is prematurely stopping the IMD or should prematurely withdraw from the clinical investigation, the investigator must perform at least one premature discontinuation visit followed by one/several follow-up visits as decided by the Sponsor and according to the circumstances.
If possible and depending the circumstance, the premature discontinuation visit will be realized on site and the follow-visit(s) could be performed by phone.
If it is not possible, the premature discontinuation visit will be performed by phone-call and/or online video consultation. In this case and if current circumstances are favorable, at least one of follow-up safety visit should be performed onsite.
During the premature discontinuation visit/phone-call, the investigator has to:

- Collect AE/SAE,
- Check the IMD compliance,
- Check the number of returned used and unused IMD,
- Instruct the patient to stop or to continue the IMD (depending on the reason as described above),
- Ensure the continuity of investigational disease medication (if appropriate),
- Perform evaluations described for the premature investigation discontinuation/final visit if possible (onsite visit),
- Prescribe to the patient the best appropriate treatment if needed,
- Collect information on concomitant medications changes.

If some follow-up visit(s) are required or if the premature discontinuation visit could not be realized on site, the investigator will have to schedule these phone-calls/visits. During this/these visit(s), the investigator has to:

- Collect AE/SAE,
- Collect information on concomitant medications changes,
- Check the IMD compliance, if applicable,
- Check the number of returned used and unused IMD, if applicable,
- Perform evaluations described for the premature investigation discontinuation/final visit if not done at the premature discontinuation visit,
- Prescribe to the patient the best appropriate treatment if needed.

In any case, the requirements for patient follow-up will be described in more details in specific guidelines which will be provided to each involved persons (investigators, Investigational team, Hospitals etc…) and to Institutions if necessary (IEC, CA etc...). This could be done by submitting a notification (in case of emergency) and/or a substantial modification.

17 PUBLICATION POLICY

By signing the CIP, the investigator agrees that the results of the clinical investigation may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the CAs will be notified of the investigator's name, address, qualifications, and extent of involvement.

The data resulting from this clinical investigation will be the proprietary information of Sponsor. An investigator shall not publish any data (poster, abstract, paper, *etc.*) without having consulted with Laboratoires THÉA in advance.

At the end of the clinical investigation, Laboratoires THÉA will prepare a Clinical Investigation Report. The draft reports will be discussed with the coordinating investigator and with Laboratoires THÉA.

For any manuscript for publication prepared by Laboratoires THÉA, Laboratoires THÉA reserves the right to select the investigators who will be the authors to review the manuscript. Laboratoires THÉA will allow the selected investigators sufficient time for full review of the manuscript before publication.

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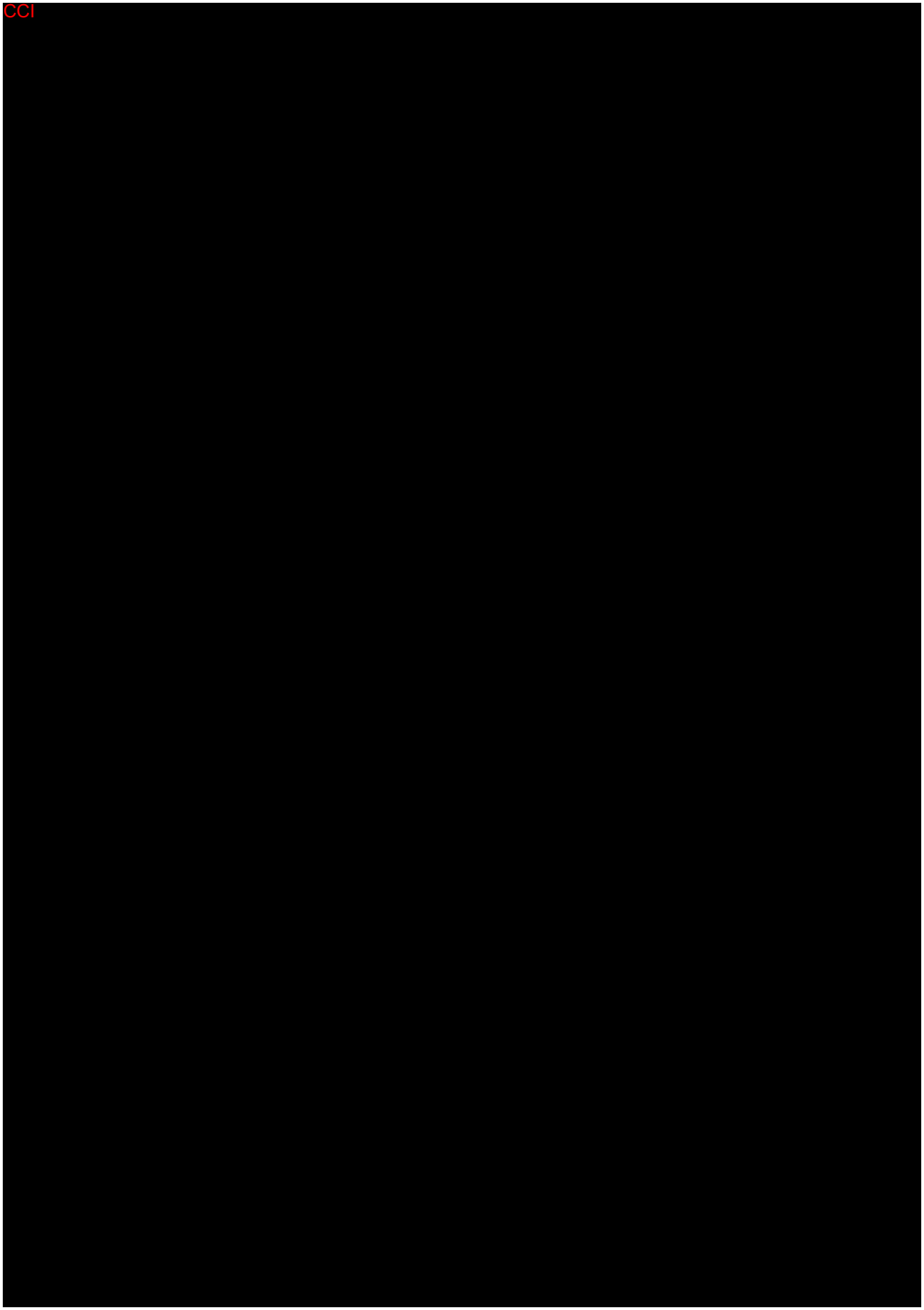
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THEALOZ TOTAL soothes the eyes from itchiness and irritations. It reduces the redness of the eyes and relieves from the symptoms of dry eyes.THEALOZ TOTAL is well tolerated on the ocular surface.

The main ingredients of THEALOZ TOTAL are trehalose and sodium hyaluronate.

Trehalose is a natural substance present in many plants and animals, which can survive in extremely dry conditions. It provides protective and hydration properties.

Sodium hyaluronate, naturally found in the human eye, holds water to hydrate and lubricate the surface of the eye. It keeps the solution on the eye surface giving long lasting relief.

The unique combination of trehalose and sodium hyaluronate in THEALOZ TOTAL offers long-lasting protection, hydration and lubrication of the eye surface.

THEALOZ TOTAL formula also includes Naaga, a medicinal substance providing soothing properties and contributing to reduce itching sensations.

The summary of safety and clinical performance is available on EUDAMED. As long as EUDAMED is not operational, this document is available upon request addressed to Laboratoires Théa.

GENERAL RECOMMENDATIONS FOR USE

Dosage: 1 drop in each eye, from 3 to 6 times daily.

There is no particular training required to use THEALOZ TOTAL.

Wash hands thoroughly before use.
Do not use any tool to open the bottle.
When you first use THEALOZ TOTAL, you will find the first drop takes longer to come out due to the unique filtration system in the bottle (see Device description).
Apply one drop in the pocket of the eyelid, while gently pulling the lower lid down and looking up and close the eye gently after application.
Replace the bottle cap after use.

OVERDOSE

No toxic effects are expected with an ocular overdose of the medicinal substance Naaga.

A topical overdose of this product may be flushed from the eye(s) with water

CAUTIONS FOR USE

Product for single patient only (multiple use).

Do not share bottles between different people to prevent cross contamination.

Check the packaging is intact before first using this product.
Check the tamper-proof ring on the bottle is intact before using it for the first time.
To avoid contamination, do not touch the tip of the bottle to any surface with anything.
You must contact a healthcare professional if your symptoms get worse or do not improve.

WARNINGS

Keep out of the sight and reach of children.

After use, do not drive or use machines if your vision is blurred: wait for few minutes that your vision recovers clear.
Wait at least 15 minutes between using two different eye products.
Never dilute THEALOZ TOTAL or mix it with other solutions.
After first use, if exposed to low atmospheric pressure, the bottle can leak.

SIDE EFFECTS

The following side effects have been reported for similar devices: rare possibility of mild eye irritation and ocular redness. In such cases, contact lens wearers should remove their contact lenses.

When you use eye drops, you might experience disturbing symptoms such as burning sensation, stinging sensation, foreign body sensation in the eye and blurred vision for a short time.

If you note any side effects or unusual sensations after using this product, please contact a healthcare professional and report the information to the local distributor, to the manufacturer or to your local Health Authority (see contacts at the end of the instructions for use).

STORAGE AND DISPOSAL CONDITIONS

Store between 8°C and 25°C.
Do not expose your product to direct sunlight or humidity.
Do not use after the expiry date, which is marked on the bottle and on the outer box.
The expiry date refers to the last day of that month as long as the packaging is intact and it has been stored correctly.
The product can be used until 3 months after first opening. After this time, discard any leftover product responsibly.
Dispose of the product responsibly and in accordance with local guidance (the bottle should be disposed of as household waste, the outercarton and the leaflet are recyclable).

Date of issue and version of the instructions for use: Ver. 8-clin 03/2023

Manufacturer:

Laboratoires Théa

12 rue Louis Blériot

63017 Clermont-Ferrand Cedex 2 France

CE 0459

www.laboratoires-thea.com

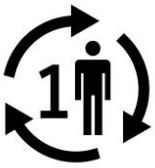
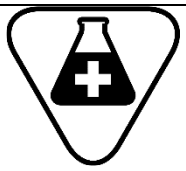
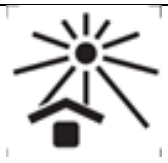
« Contact us » section

Distributors:

[Country]: Local distributor name and address

Health authorities:
[Country]: Health authority name and address

MEANING OF THE PICTOGRAMS ON THE PACKAGING

	**Manufacturer**		**Medical Device**
	Batch number		Consult instruction for use
	Date of manufacture		Single patient – Multiple use
	Use-by date		Do not use if package is damaged
	Temperature limits		Caution
	Sterilized using aseptic processing techniques		Contains a medicinal substance
	Unique Device Identification		Catalogue number
	Keep away from sunlight		Keep dry
	Single sterile barrier system with protective packaging outside		

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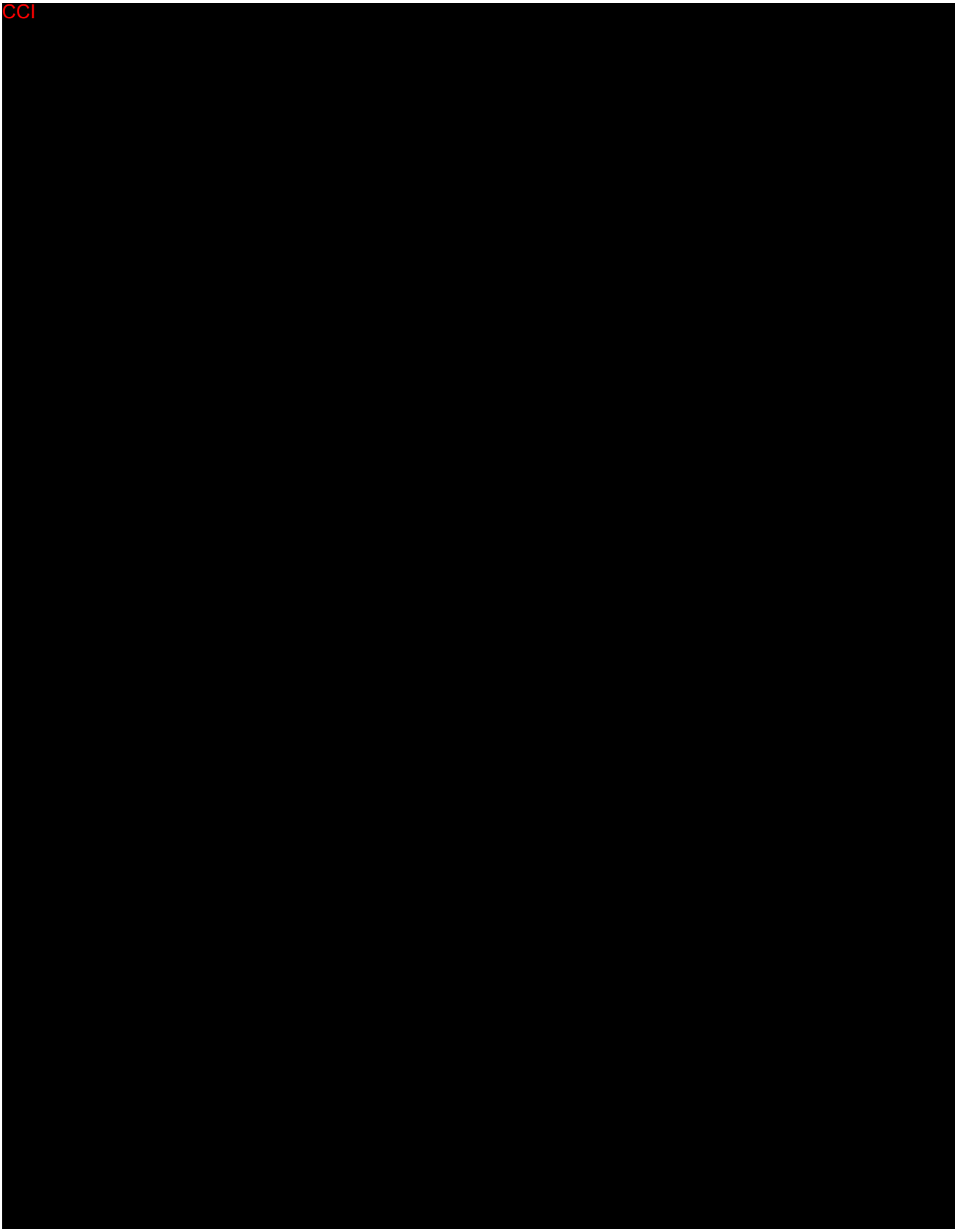

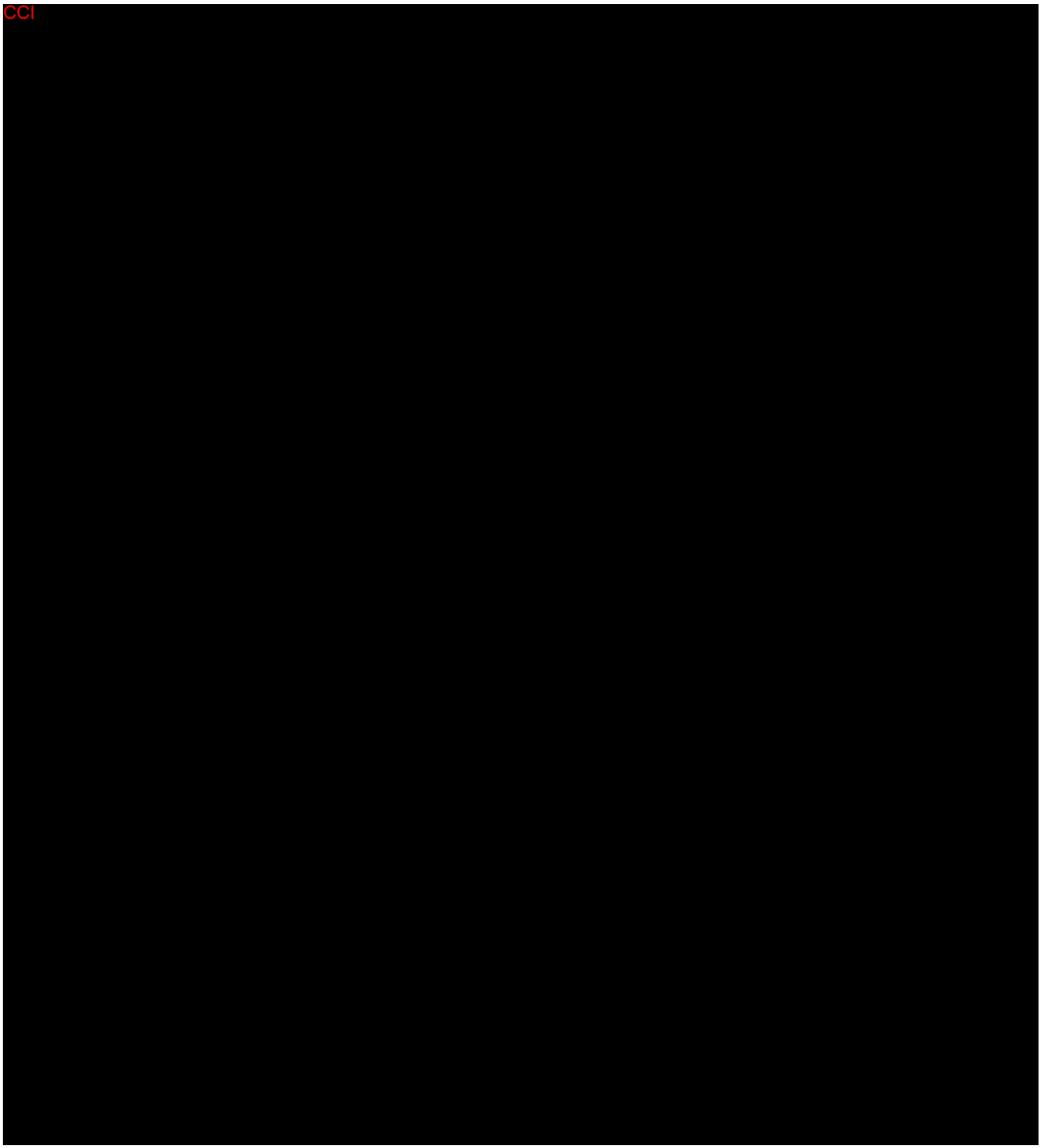
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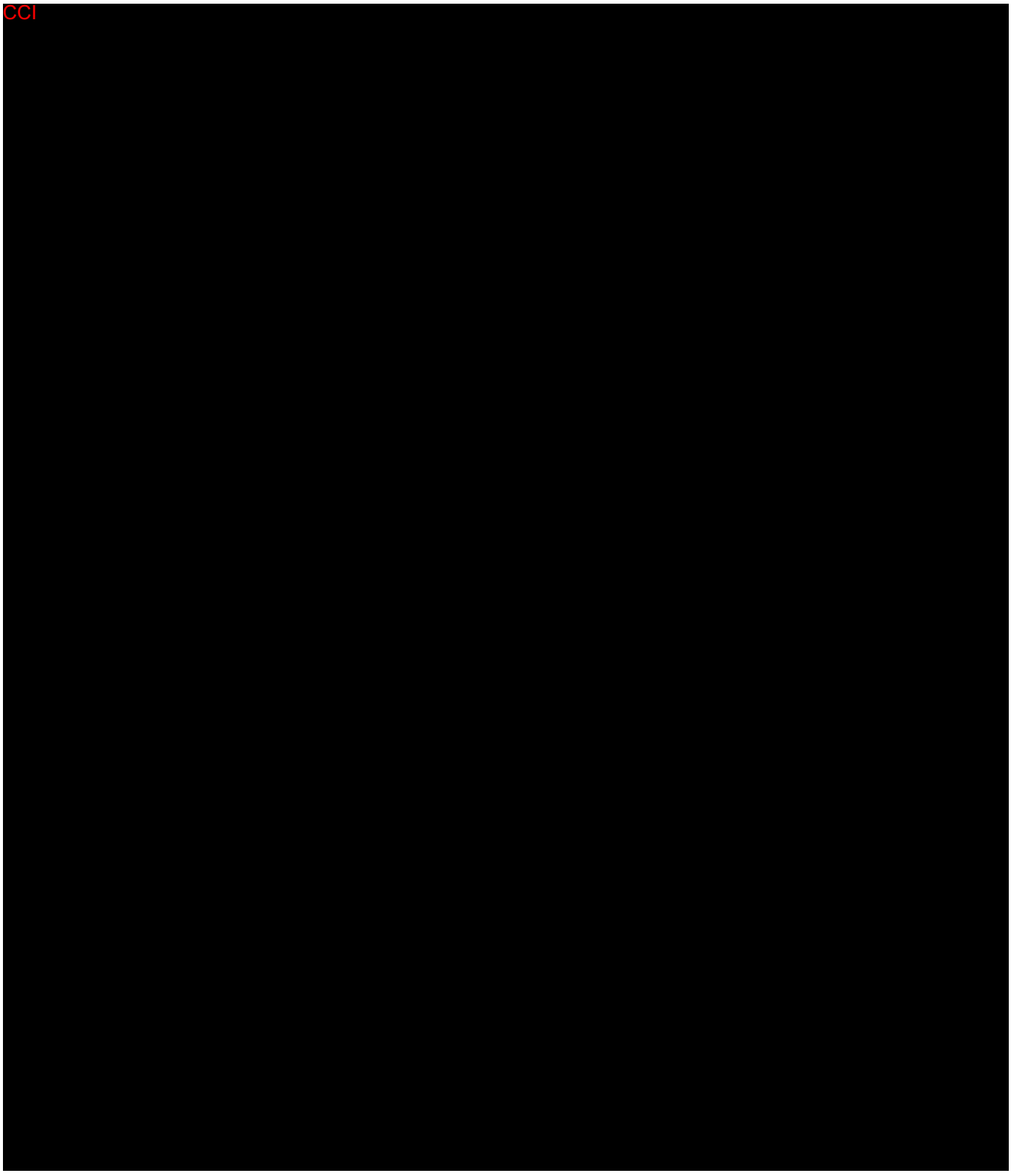

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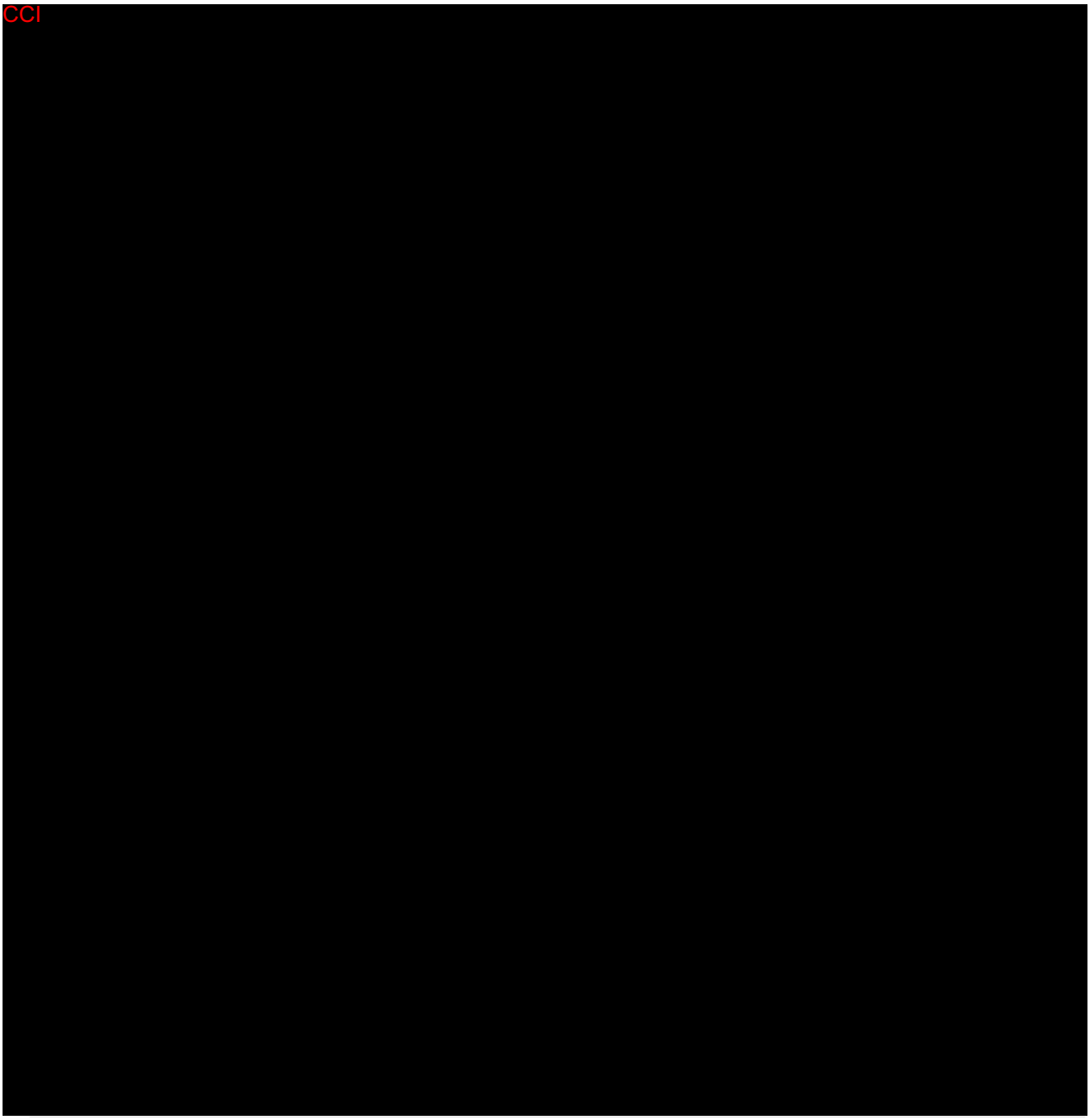
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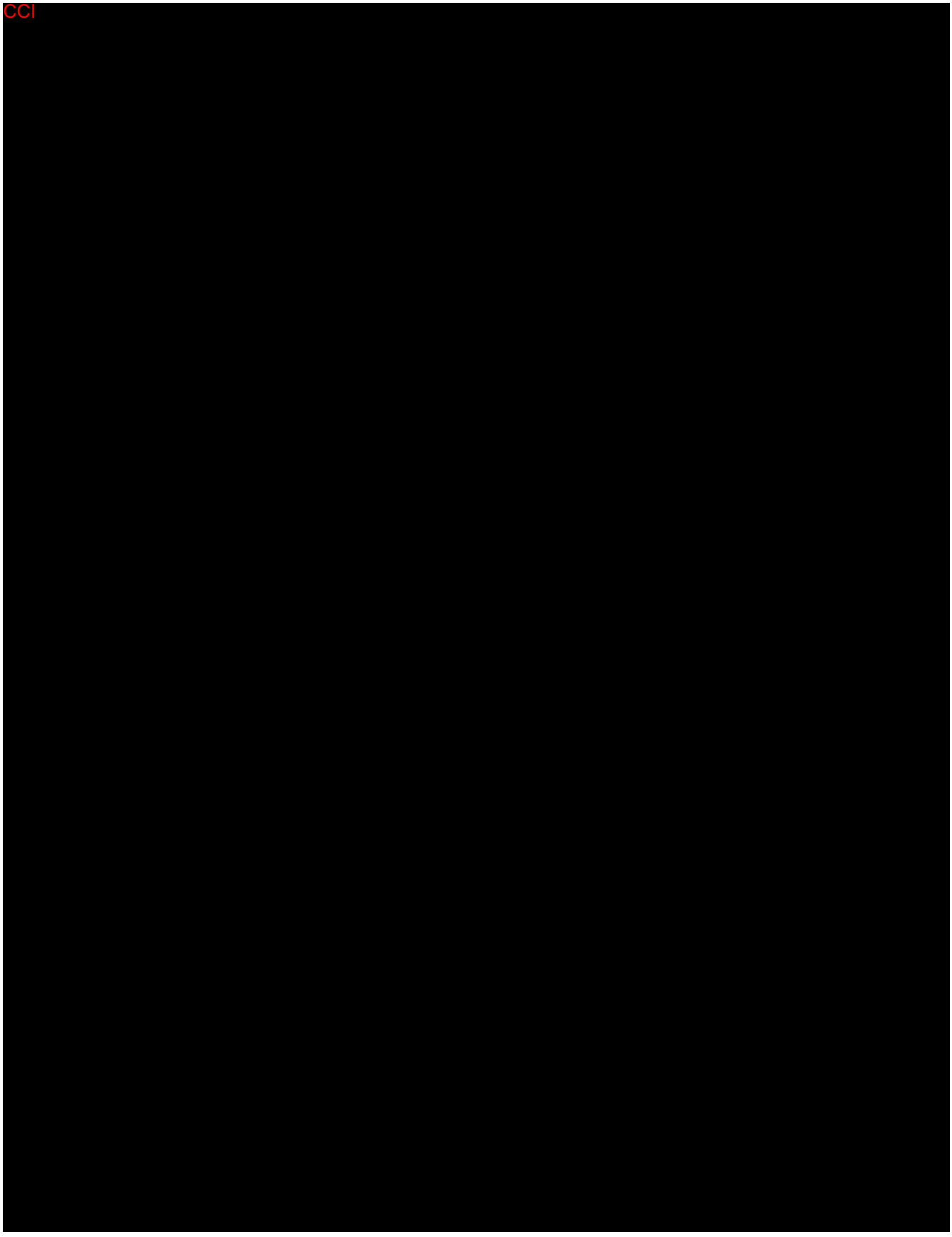

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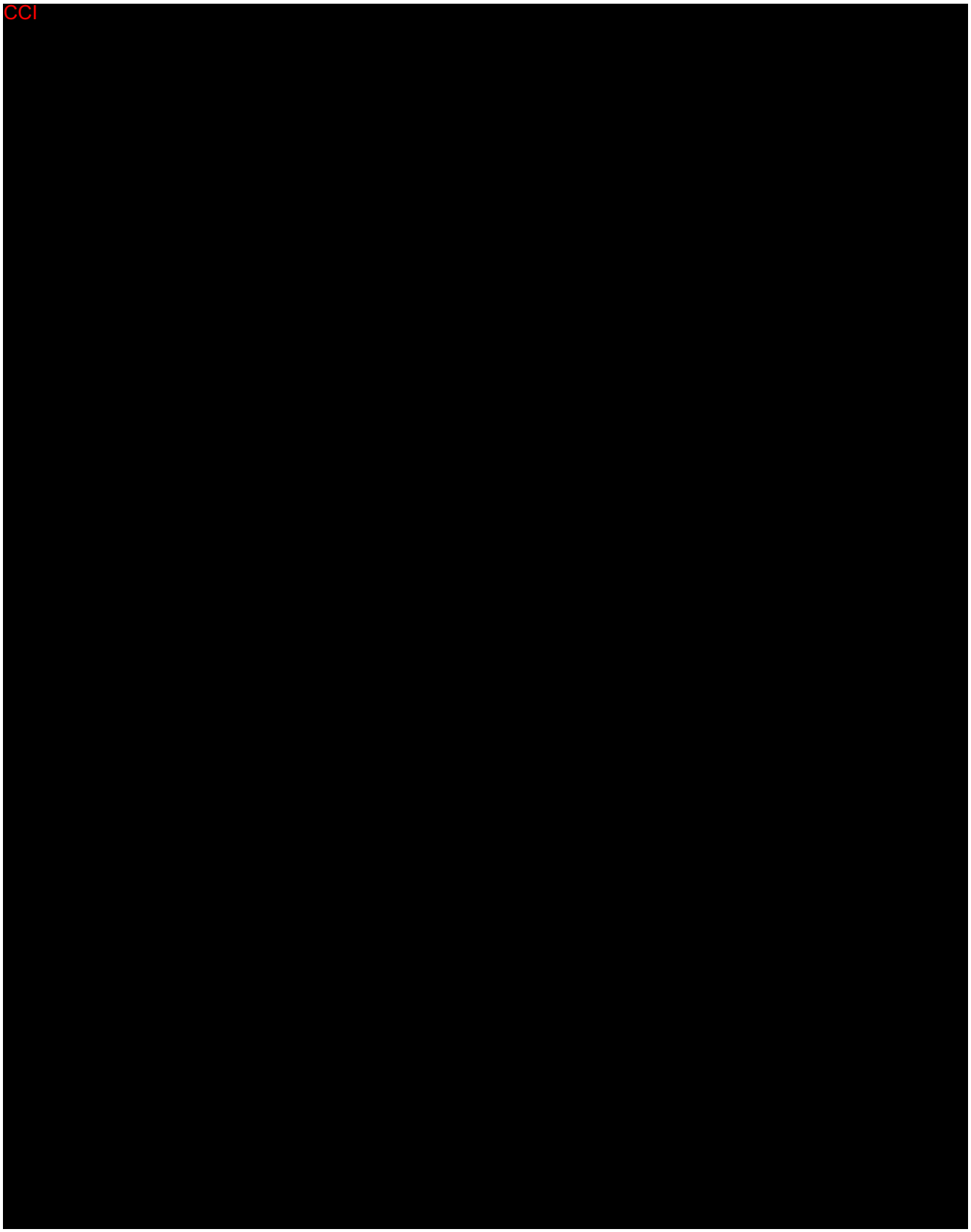

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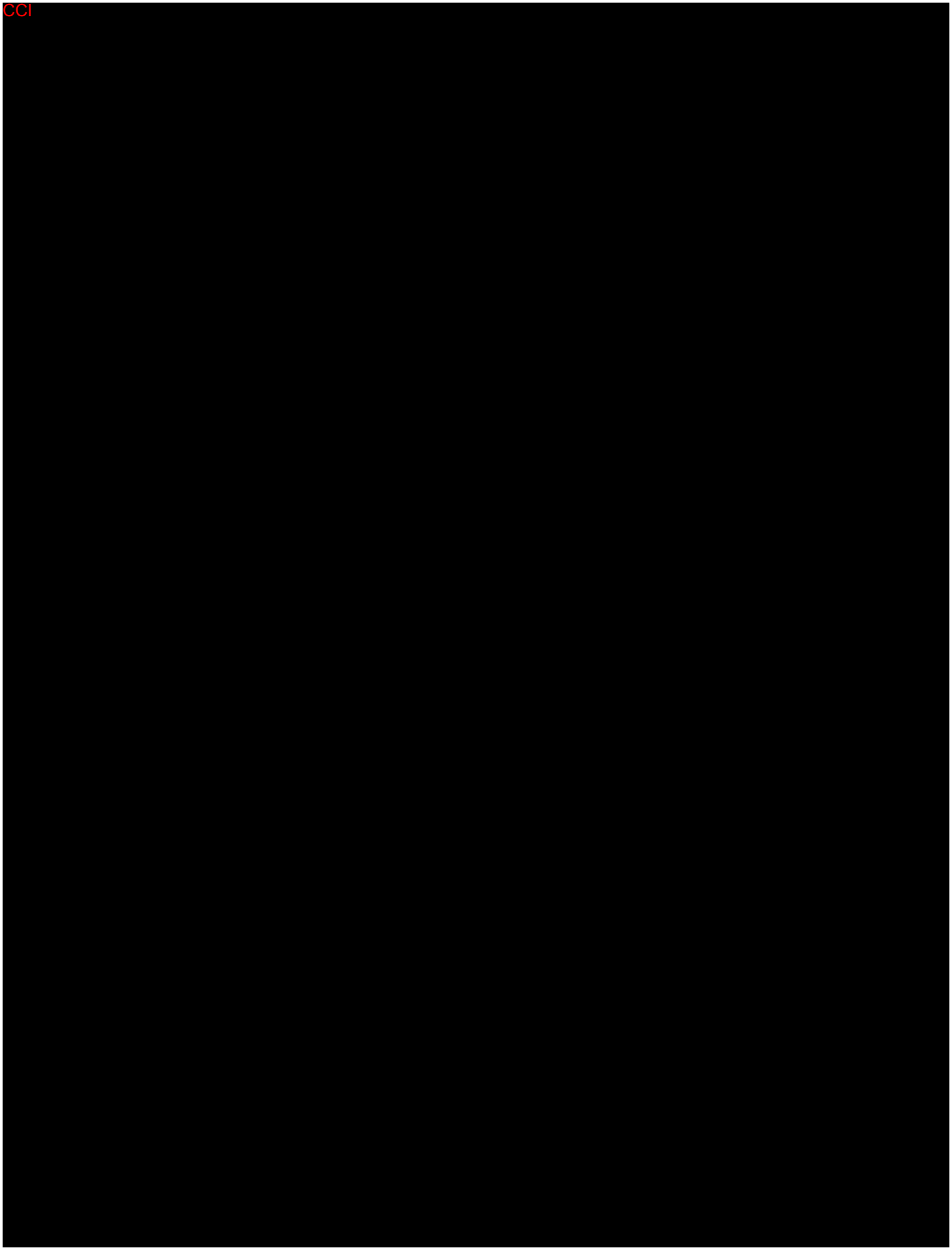

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