1. GENERAL

1.1. IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN

1.1.1 Clinical Investigation References

CLINICAL INVESTIGATION PLAN

Investigation No. LT2769-002

the clinical investigation will be registered in Clinicaltrials.gov

Initial Clinical Investigation Plan:	Version 1.0 dated 04.04.2023
Current Clinical Investigation Plan:	Version 2.0 dated 15.06.2023

1.1.2 CIP Amendments

TITLE: Comparison of the performance and safety of T2769 versus Vismed® Multi in the treatment of moderate to severe Dry Eye Syndrome.

LABORATOIRES THÉA

Clinical Investigation Plan (CIP) No.:	LT2769-002
Investigational Medical Device (IMD):	T2769
Indication:	Moderate to severe dry eye syndrome
International Coordinating Investigator:	[redacted]
Sponsor's Medical Expert:	[redacted]

This confidential clinical investigation plan is the property of Laboratoires THÉA. No unpublished information contained herein may be disclosed without prior written approval of Laboratoires THÉA.

1.1.3 Abbreviations and Acronyms

ADE	Adverse Device Effect
AE	Adverse Event
ALCOCCEA	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available
ANOVA	Analysis of variance
ASADE	Anticipated Serious Adverse Device Effect
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 Investigation Report
[redacted]	[redacted]
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
CRO	Contract Research Organisation
DD	Device Deficiency
DED	Dry Eye Disease
DES	Dry Eye Syndrome
DEWS	Dry Eye Workshop
DMP	Data Management Plan
e-CRF	Electronic Case Report Form
EDTRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IA	Interim Analysis
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions For Use
IMD	Investigational Medical Device
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
KSC	Keratoconjunctivitis Sicca
LFU	Lacrimal Functional Unit
[redacted]	[redacted]
LS	Least Squares Means
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]

MMRM	Mixed Model for Repeated Measures
NA	Not applicable
NRS	Numeric Rating Scale
OSDI	Ocular Surface Disease Index
PP	Per Protocol
QoL	Quality Of Life
Q1	First Quartile
Q3	Third Quartile
[redacted]	[redacted]
RMP	Risk Management Plan
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SH	Sodium Hyaluronate
SOC	System Organ Class
SOTA	State Of The Art
TBUT	Tear Break Up Time
TEAE	Treatment Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
WHODrug	World Health Organisation Drug dictionary

1.2.SPONSOR

Laboratoires THÉA
Research and Development Department
[redacted]

Sponsor contact: Laboratoires THÉA - Research and Development Department

First Name - Name/function	Details
[redacted] Clinical Development Director	[redacted]
[redacted] Medical Development Director	[redacted]
[redacted] Clinical Operation Manager	[redacted]
[redacted] Biometrics Manager	[redacted]
[redacted] Safety & Medinfo Manager	[redacted]
[redacted] Clinical Project Leader	[redacted]

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

1.3.1 Investigators details

The Sponsor will maintain an updated list of Principal Investigators and investigation sites, 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

Name and Functions	Details
Regulatory Submissions, Monitoring, Project Management, Data-Management, Statistics	[redacted]

STATEMENT OF THE SPONSOR AND OF THE COORDINATING INVESTIGATOR

Comparison of the performance and safety of T2769 versus Vismed® Multi in the treatment of moderate to severe Dry Eye Syndrome.

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 14155:2020.

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

INTERNATIONAL COORDINATING INVESTIGATOR

[redacted] 26/06/2023
First Name - Name *date*

[redacted]

SPONSOR: LABORATOIRES THÉA

Medical Operations Director

[redacted] 20/06/23
First Name - Name *date*

[redacted]

Clinical Development Director

[redacted] 20/06/2023
First Name - Name *date*

[redacted]

Biometrics Manager

[redacted] 26/06/2023
First Name - Name *date*

[redacted]

INVESTIGATOR SIGNATURE PAGE

Comparison of the performance and safety of T2769 versus Vismed® Multi in the treatment of moderate to severe Dry Eye Syndrome.

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 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 last device has been placed on the market)
- Ensure that all people assisting with the investigation are adequately informed about the CIP, the IMD(s) and their trial-related duties and functions
- Confirms that I have read this CIP and that I agree to comply with all parts or items.

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

INVESTIGATIONAL SITE

Principal Investigator

First Name - Name	*date*	*signature*

SPONSOR: LABORATOIRES THÉA

Clinical Project Leader

[redacted]	20/06/2023	[redacted]
First Name - Name	*date*	

TABLE OF CONTENTS

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 and on the labels on the IMD boxes.

Test device: T2769 (Thealoz Total)

T2769 is a sterile, phosphate-free and pH neutral solution. It contains Trehalose, Sodium Hyaluronate (SH) and Naaga.

T2769 device is presented in the ABAK® multi-dose bottle (12.5 mL).

As per Instructions For Use (IFU), T2769 is indicated in case of moderate to severe dry eye syndrome.

Comparative device: Vismed® Multi

Vismed® Multi*:* eye drops presented in multi-dose container. It contains SH.

Vismed® Multi is recommended for moderate and severe dry eye conditions.

2.2.DETAILS CONCERNING THE MANUFACTURER OF THE IMD.

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

2.3.PACKAGING AND LABELLING

2.3.1 Packaging

The IMD and Hydrabak® will be packaged by approved contractor. in accordance with ISO 14155 and Regulation (UE) 2017/745. The IMDs will be prepared according to the packaging list provided by the statistician.

Hydrabak® is supplied in the ABAK® 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.

T2769 is packaged in a multidose white polyethylene ABAK® 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:

Each patient will receive 1 preservative-free multidose bottle of Hydrabak® (ABAK system) during the run-in period and 4 preservative-free multidose bottles of the IMD during the investigation.

2.3.2 Labelling

All labels will be written in the local language. The content of the labelling is in accordance with ISO 14155 and Regulation (UE) 2017/745 specifications and requirements.

Each bottle of run-in treatment and IMD will carry one label.

The carboard box of Hydrabak will also carry a detachable label (flag label) bearing at least the CIP number and the batch number.

The cardboard carton of IMD will also carry a detachable label (flag label) bearing at least the CIP number and IMD 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 in order to record the dispensing procedure.

2.4. INTENDED PURPOSE OF THE IMD IN THE PROPOSED CLINICAL INVESTIGATION

T2769 is intended to hydrate and soothe itchy, red or irritated eyes in case of moderate to severe dry eye syndrome (patients over or equal than 18 years excluding pregnant or breastfeeding women).

2.5. THE POPULATIONS AND INDICATIONS FOR WHICH THE IMD IS INTENDED

T2769 is suitable for adults.

2.6.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, Na 2.45%), NaOH 0.1N, Water for injections and Nitrogen.

T2769 is a sterile, phosphate-free and pH neutral solution.

The solution is supplied in the ABAK® 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

T2769 should be used within 3 months after first opening of the ABAK® container.

Table 3 Investigational Medical Device T2769

Names of ingredients	Percentage formula (g/100 ml)	Function	Reference to standards
Trehalose dihydrate*	3.00*	Lubricating, hydrating agent	Current Eur. Ph. [2297]
N-acetyl aspartyl glutamic acid, sodium salt (NAAGA, Na)*	2.45*	Soothing agent	[redacted]
Sodium hyaluronate**	0.15*	Lubricating, hydrating agent	Current Eur. Ph. [1472]
NaOH 0.1N***	qsp pH 7.2	pH adjustment	Current Eur. Ph. [0677]
Water for injections	qsp 100 ml	Vehicle	Current Eur. Ph. [0169]
Nitrogen	-	Ad preparation and storage	Current Eur. Ph. [1247]

* *The quantity of the ingredient (Trehalose dihydrate and Naaga Na) is adjusted as a function of its titre and water content*

** *The quantity of this ingredient is adjusted as a function of its water content*

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

The excipients of the T2769 eye-drops (NaOH, water for injections and Nitrogen) 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.

2.7.STORAGE CONDITIONS AND INSTRUCTIONS 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.

Do not refrigerate or freeze.

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 product can be used until 24 months before opening and 3 months after first opening. The expiry date refers to the intact correctly stored packaging.

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

If significant changes and/or update on labelling, handling and storage are required during the 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.

2.8.INVESTIGATOR BROCHURE AND INSTRUCTIONS FOR USE

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 writing the CIP, validated and applicable versions are

- For the IB: V3, MAR-2023
- For the IFU: V8, MAR-2023

2.9.DESCRIPTION OF COMPARATIVE DEVICE

Vismed® Multi is purchased from Horus Pharma.

Vismed® Multi is a sterile solution for ocular use.

Packaging and labelling are provided in Section 2.32.3.

Batch number and expiration dates will be specified on the packaging.

Storage conditions are specified in **Section 2.7**.

Table 4 Vismed® Multi details the composition and function of the comparative device Vismed® Multi.

Table 4 Vismed® Multi

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

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

[redacted]

3.4 DESCRIPTION OF THE CLINICAL DEVELOPMENT STAGE

The investigation is defined as a pre-market, pivotal 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

4.3 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 the following:

- The device is not biocompatible (use of the device beyond the expiry date)

- The product is not sterile (loss of the sterile barrier due to inappropriate storage conditions by the user)

- The device is contaminated (the user lets the tip of the container touch something (eye, eyelid, objects, user's hand OR the user shares the device with another person (cross contamination))

- The device leaks (primary packaging deterioration due to inappropriate storage conditions)

- The patient gets hurt while using the device (the user uses a sharp object to remove the cap/open the device and damages the device and/or gets hurt OR the patient drives or uses machines while experiencing blurred vision)

- Continuous use of the device is not ensured (the user uses another product by mistake)

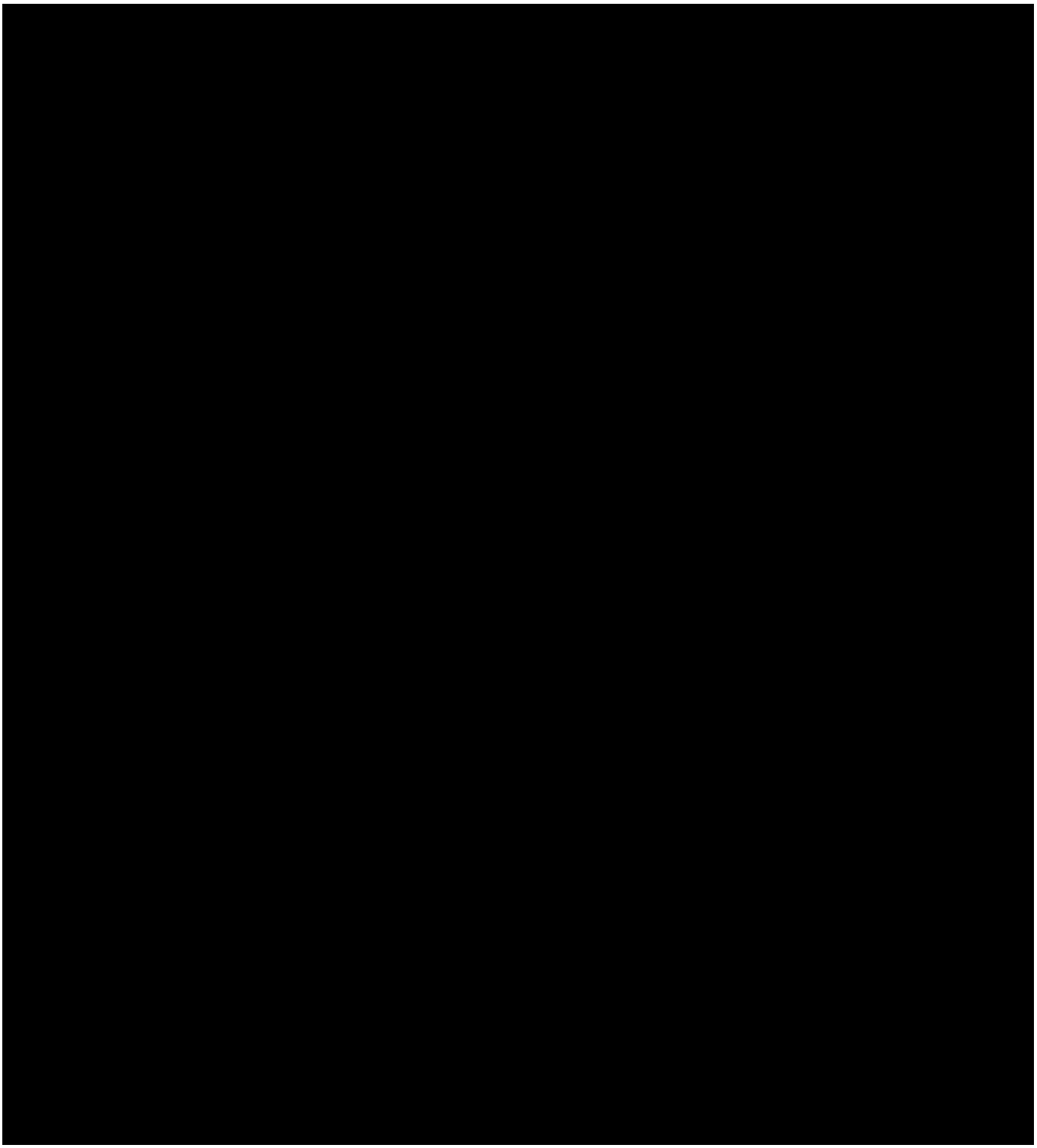
- A child swallows a component of the device (bottle cap)

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 should be asked to wait at least 15 minutes between using two different eye products.



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 of THEALOZ TOTAL 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:

- THEALOZ TOTAL improvement of (global) ocular comfort

5.2 OBJECTIVES, PRIMARY [redacted]

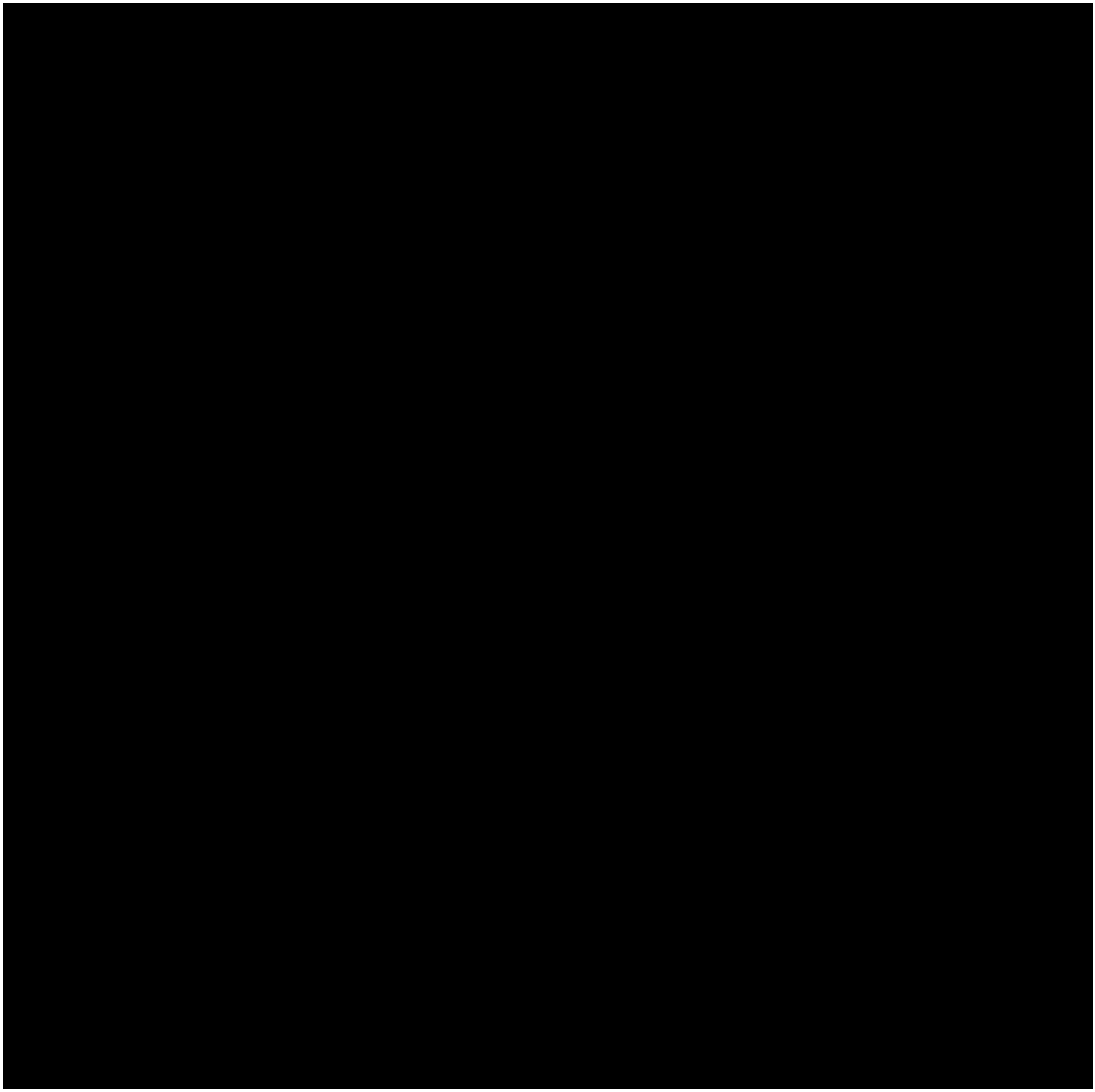
The primary objective of the investigation is to demonstrate the non-inferiority of T2769 *versus* Vismed® Multi in terms of total ocular surface staining (Oxford score) in patients with DES, after 35 days of treatment.

[redacted]

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

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

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



6. DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

6.1.1 Justification of the Investigation Design

Methodology: A 5-week, international, multicentre, randomised, investigator-masked, 2 parallel groups (T2769 versus Vismed® Multi) investigation in DES patients.

- Multicentre investigation

The investigation will be performed in different sites in EU and outside EU.
Multicentre (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.

- Randomised

At the randomisation visit on Day 1, patient fulfilling all eligible criteria will be randomly assigned to 1 of the 2 treatment groups. Randomisation allows keeping the investigator's masking about the product use for DES treatment. It is generally considered the most reliable method for evaluating the effects of interventions.

- Choice of run-in period

Patients meeting the screening criteria will undergo a 7-10-day run-in period. During this period, all patients will substitute their current treatment with Hydrabak®, ophthalmic solution containing NaCl 0.9%. [redacted]

- Investigator-masked

A double-masked investigation design is not possible due to different commercial packaging between T2769 – Vismed® Multi.

However, the identity of the IMD given to each patient will not be known for the masked investigator who is independently in charge of the ophthalmic examination.

To this aim, the masked investigator will differ from the person who will record the used/unused IMDs. The recording will be delegated either to the hospital pharmacy or to a trained collaborator (trained by the masked investigator; hereafter referred to as unmasked collaborator). Therefore, the masked investigator should not receive the returned IMDs from the patients.

[redacted]

[redacted]

- Scheme of administration

The dose regimen recommended is 3 to 6 times daily.

[redacted]

- Choice of primary endpoint [redacted]

The primary [redacted] endpoints of this clinical study (total ocular surface staining (Oxford scale), [redacted] have been taken into consideration based on the clinical literature review (Jones et al. 2017; Aragona et al. 2019; Fariselli et al. 2018; Mateo Orobia et al. 2017; Nasser et al. 2018; Pinto-Bonilla et al. 2015; Chiambaretta et al. 2017). Consequently, these endpoints are clinically relevant, clearly defined and assessed at specified time points in order to provide clinical evidence on the efficacy [redacted] of T2769 in its intended use (i.e., improvement of the ocular signs and symptoms in DED patients).

- Symptom assessment

Ocular symptoms (except upon instillation, not assessed at inclusion) 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*

A randomised design has been chosen to ensure a balanced allocation to the assignment of device arms of all patient's known and unknown characteristics. Randomisation helps to avoid possible bias in the selection and allocation of patients arising from the predictability of device assignments.

The randomisation code list stratified by site and lists of IMDs numbers for the packaging is generated by the Interactive Web Response System (IWRS) provider. Patients will be randomised on a 1:1 basis to T2769 or Vismed® Multi respectively.

Randomisation list(s) and lists of IMDs numbers for the packaging are to be kept in security by the editor (IWRS provider) according to their procedures.

The packaging list is to be kept by the company responsible for manufacturing and labelling of the treatment unit.

The randomisation and the IMD kit number will be allocated to the patients according to randomisation list using an Interactive Response Technology (IRT).

Randomisation will occur at Randomisation visit (Day 1; Visit#2) after all procedures have been performed and eligibility for the investigation confirmed. The patient who meets the eligibility criteria will be randomly assigned to treatment and associated to a randomisation number.

6.1.2.2 Masking and Code Breaking

Serious biases may occur in a clinical investigation including investigator bias (which may arise due to knowledge by the investigator of treatment allocated to a particular patient), evaluator bias and placebo effects. To protect an investigation against these potential biases, masking will be used.

This will be an investigator-masked clinical investigation.

The **masked investigator** will remain masked to the IMD (T2769 – Vismed® Multi). He/She will not receive the returned IMD from the patients.

The following-up and the number of returned IMDs will be recorded by **unmasked collaborator** throughout the clinical investigation.

The unmasked collaborator will also be in charge of returned/unreturned IMD (T2769 – Vismed® Multi) counting.

Masking will be achieved by coding the interventions, providing each product unit with identical cardboard box and by identifying it by an IMD kit number.

The code should not be broken except:

- in case of medical emergency (where knowledge of the IMD received would affect the treatment of the emergency),
- or when it is a regulatory requirement (*e.g.*, for Unanticipated Serious Adverse Device Effect [USADE]).

The investigator is responsible for accessing the IRT System to obtain the name of the IMD received by the patient.

If an emergency code breaking becomes necessary, the investigator should notify the Sponsor.

When a code is broken, the date, time and reason must be recorded in the patient's Source~~,~~ and in any associated AE report. The identity of the IMD should not be disclosed in these documents.

Further to a USADE assessment by the Global Drug Safety & Medical Information Department, the code might be broken for reporting purposes. The relevant Laboratoires THÉA, Contract Research Organization (CRO) and masked investigator and masked staff remain unaware of the identification of the IMD as per the above-mentioned process.

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

6.1.2.3 Dispensing

IMD will be dispensed by the masked collaborator and/or pharmacist delegate for selected tasks. Each IMD dispensation will be recorded in the related documentation.

During the whole investigation treatment period, the **masked investigator and/or delegate** will remain masked to the IMD (T2769 – Vismed® Multi). He/she will not receive the returned IMD from the patients.

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 Clinical Investigational Plan (CIP) and the randomisation.

Once all screening criteria have been checked, the patient will receive a box including Run-in Hydrabak® treatment for the run-in period.

At the randomisation visit#2 (Day 1), once inclusion and exclusion criteria have been checked and once the patient is eligible, the randomisation will be performed and the IRT will provide the IMD kit number allocated to the patient.

At the other visit (visit#3, Day 15 days±1 day after the randomisation) with dispensation, the IRT will provide the IMD kit number allocated to the patient.

Two dispensations will be performed as follows:

- At randomisation visit#2(Day 1): one box containing enough bottles for the treatment period Day 1 to Day 15 ± 1 day will be provided by the investigator (or delegate) or pharmacist with the number assigned by the IRT.

- At Visit#3 (Day 15): one box containing enough bottles for the treatment period Day 15± 1 day to Day 36 + 3 days will be provided by the investigator (or delegate) or pharmacist with the number assigned by the IRT.

The site team member will instruct patient on the method of instilling the doses and will train his / her patient to not disclose the IMD characteristics neither during the visit not when reporting / discussing AE / Device Deficiency (DD).

6.1.3 Primary [redacted], with rationale for their selection and measurement

6.1.3.1 *Primary performance endpoint*

The primary performance endpoint is the change from baseline in total ocular surface staining. It is the most commonly used endpoints in clinical trials with DED patients. It is performed to detect ocular damage surface, which is considered as a hallmark sign of DED.

Thus, the change from baseline (Day 1) in total ocular surface staining grade according to Oxford 0-15 grading scheme (corneal and conjunctival staining by fluorescein with a yellow filter) at D36 in the study eye was set as the primary performance endpoint to evaluate the performance of the treatment.

[redacted]

Different ocular surface staining scales have been developed and despite common usage, a universally accepted “gold standard” grading scale does not exist for corneal and conjunctival staining. This investigation will use the Oxford scale, a widely used and standardised grading scale. International regulatory agencies such as the Food and Drug Administration (FDA) rely on corneal and conjunctival staining measurement as a primary endpoint in clinical trials of commercially registered dry eye treatments (Begley et al. 2019).

[redacted]

6.1.3.3 *Safety endpoints*

The following safety and tolerability endpoints will be assessed:

[redacted]

- Ocular and systemic TEAE,
- Ocular and systemic Serious TEAE,
- Ocular and systemic TEAE leading to premature IMD discontinuation,
- Ocular and systemic IMD related TEAE

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

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

Visit #1: Day 1-10/Day 1-7 Screening visit (run-in period)

Visit #2: Day 1 Randomisation visit (D1)

Visit#3: Day15 (±1 day) (D15)

Visit #4: Final visit Day 36 (+3 days) or premature discontinuation visit.

Visits should be performed at the same hour (±4 hours)

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

Screening Period

Visit#1: Screening visit (Day1-10/Day1-7)

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

Visit#1 will consist of the following procedures by the masked investigator or authorised delegate who will perform the ophthalmologic examination during all the visits.

By the masked investigator or delegate for selected tasks (according to local requirements, the investigator may delegate tasks to collaborator)

- Information for the patient and signature of the consent (can be done up 7 days before this visit). See **Section 13**.

  ✓ On paper CRF
- Ocular discomfort (VAS)

  ✓ On eCRF
- Demography
- History of dry eye
- Urine pregnancy testing
- Questioning about ocular and systemic medical and surgical history (other than dry eye)
- Questioning about previous and concomitant ocular and non-ocular treatments
- Measurement of Far BCVA
- Questioning about ocular symptoms within the last 48 hours
- Slit lamp examination for measuring*:
  - Measurement of conjunctival hyperaemia with [redacted] photographic scale
  - TBUT

  - Oxford 0-15 grading scheme (corneal and conjunctival staining by fluorescein with a yellow filter)
- Schirmer test without anaesthesia,
- Verification of inclusion and exclusion criteria,
- Status of the patient, (start of run-in period or not),
- Run-in treatment dispensation,
- Patient diary dispensation (instructions)**.

* Examination must be performed by the masked investigator or delegate for selected tasks for all visits and using the same slit lamp.

** The patient diary will be an aid to compliance assessment, it will not be recorded in the database.

The next visit must be scheduled between 7 and 10 days after Visit#1 at the same hour (± 4 hours).

Treatment Period

Visit#2: *Randomisation visit* (Day 1)

Visit#2 will consist of the following procedures and examinations to be done according to the following order and in each eye.

Visit#2 will consist of the following procedures and examinations by the masked investigator or authorised delegate who will perform the ophthalmologic examination during all the visits.

By the masked investigator (the same as the screening visit) **or delegate for selected tasks** (according to local requirements, the investigator may delegate tasks to collaborator)

✓ On paper CRF

- Questionnaire (OSDI)
- Ocular discomfort (VAS)

✓ On eCRF

- Questioning about ocular symptoms within the last 48 hours
- Questioning about Hydrabak® compliance during run-in period and last instillation (at least 6 hours) before the visit and check of the patient diary completion with the patient,
- Questioning about previous and concomitant ocular and non-ocular treatments
- Slit lamp examination for measuring*:
  - Measurement of conjunctival hyperaemia with [redacted] photographic scale
  - TBUT
  - Oxford 0-15 grading scheme (corneal and conjunctival staining by fluorescein, with a yellow filter),
- Schirmer test* (without anaesthesia),
- AE reporting
- Verification of inclusion and exclusion criteria
- Status of the patient
- Randomisation
- IMD dispensation

- Patient diary dispensation. The patient who will be instructed to instil the IMD in both eyes and report in the patient diary the number of instillations/day and to bring back it at each visit.

* Examination must be performed by the same **masked investigator or delegate for selected tasks** for all visits and using the same slit lamp.

The next visit must be scheduled in 15 days (±1 day) at the same hour (± 4 hours).

Visit#3: Day 15 (±1 day)

Visit#3 will consist of the following procedures and examinations to be done according to the following order and in each eye.

By the masked investigator (the same as the screening visit) **or delegate for selected tasks** according to local requirements, the investigator may delegate tasks to collaborator)

✓ On paper CRF

- Questionnaire (OSDI)
- Ocular discomfort (VAS)

✓ On eCRF

- Questioning about ocular symptoms upon instillation
- Questioning about ocular symptoms within the last 48 hours
- Questioning about soothing sensation 15 min after IMD instillation
- Assessment of global patient satisfaction with the use of bottle
- Assessment of global satisfaction by the patient
- Assessment of the ocular tolerance by the patient
- Questioning about ocular and non-ocular concomitant treatments
- Review of the completion patient diary
- Questioning about IMD dose regimen compliance
- Slit lamp examination for measuring*:
  - Measurement of conjunctival hyperaemia with [redacted] 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 deficiency
- Assessment of the ocular tolerance by the investigator
- Assessment of the performance by the investigator

* Examination must be performed by the same **masked investigator or delegate for selected tasks** for all visits and using the same slit lamp.

By the unmasked collaborator:

- Recording the number of returned used and unused IMD in document source (the accountability is expected for the amount of bottles) and transfer this information to masked investigator.

The next visit must be scheduled at Day 36 later (+3days)

Visit#4: Day 36 (+3days)

Visit#4 will consist of the following procedures and examinations to be done according to the following order and in each eye.

By the masked investigator (the same as the screening visit) or delegate for selected tasks

(according to local requirements, the investigator may delegate tasks to collaborator).

✓ On paper CRF

- Questionnaire (OSDI)
- Ocular discomfort (VAS)

✓ On eCRF

- Questioning about ocular symptoms upon instillation questionnaire
- Questioning about ocular symptoms within the last 48 hours
- Questioning about soothing sensation 15 min after IMD instillation
- Assessment of global patient satisfaction with the use of bottle
- Assessment of global satisfaction by the patient
- Assessment of the ocular tolerance by the patient
- Questioning about ocular and non-ocular concomitant treatments
- Measurement of Far Best Corrected Visual Acuity,
- Review of the completion patient diary
- Questioning about IMD dose regimen compliance
- Slit lamp examination for measuring*:
  - Measurement of conjunctival hyperaemia with [redacted] 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 deficiency
- Assessment of the ocular tolerance by the investigator
- Assessment of the performance by the investigator
- Status of the patient

* Examination must be performed by the same masked person for all visits and using the same slit lamp.

By the unmasked collaborator:

- Recording the number of returned used and unused IMD in source document (the accountability is expected for the amount of bottles),and transfer this information to masked investigator.

Premature discontinuation Visit during the 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 course of the study, the patient has to inform the investigator. Either the patient may continue the investigation when he/she can follow the protocol requirements safely and in accordance with the national/regional recommendations or the patient may be withdrawn from the investigation. The last site visit should take place as soon as possible after the patient stops taking IMD.

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

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

If the patient withdrew from the investigation due to an exceptional circumstance, and if an onsite visit was not authorised, 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 medication as per routine clinical practice
- Collect AE/Serious Adverse Event (SAE) and any changes in concomitant treatments
- Collect DD
- 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

Safety Follow-up visit on site[1]

During the onsite follow-up visit done 4 weeks later (±7 days) after the premature discontinuation phone call, the following procedures are required:

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

6.1.5 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 primary endpoint "Total ocular surface staining grade".
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 study, the monitor should verify that the maintenance is performed (cf. manufacturer guidelines).
During the study, the same slit lamp must be used for the same patient at each protocol visit.

6.1.6 Procedures for the Replacement of Patients

The number of randomised patients will be followed in order to obtain at least 226 evaluable patients in the FAS population.

6.1.7 Investigation Sites

Patients are to be enrolled in approximately 40 investigational sites in 9 countries.

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

6.1.8 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.

[1] If a safety onsite visit is still not possible, the follow-up will be done by phone 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.

6.2 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 at least 2 hours before Visit#3 and 4. However, the first instillation can be done any time after the patient has completed the randomisation visit.

There will be two treatment groups:

- T2769 (test device)
- Vismed® Multi (reference device)

A detailed description of T2769 and of Vismed® Multi is available in **Section 2**.

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

Run-in Treatment/Wash-out Treatment

Once all screening criteria have been checked, the patient will receive a box containing 1 bottle of Hydrabak® treatment for the run-in period between Day-10/-7 to Day 1. 1 drop in each eye 3 to 6 times daily

Hydrabak® is an unpreserved NaCl 0.9% ophthalmic solution supplied in a 10 ml multidose ABAK® system bottle. Hydrabak® will be provided by Laboratoires Théa.

Table 6 Run-in Medical Device Sodium Chloride (Hydrabak®)

Ingredient	**Function**	**Percentage formula (g/100 mL)**
Sodium Chloride	Isotonising agent	0.900
Disodium phosphate rate	pH Buffer	0.317%
Sodium dihydrogen phosphate	pH Buffer	0.067%
Water for injections	Vehicle	*Ad 100 mL*

Batch number and expiration dates will be specified on the packaging.

Auxiliary Products

An auxiliary product is defined as a product used on site 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 each visit to perform the slit lamp examination: TBUT and Corneal 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).

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

6.2.4 Justification

During the investigation, each patient will receive 1 bottle of Hydrabak® and the IMD (4 bottles of T2769 or of Vismed® Multi) to cover run-in and active treatment period.

6.3 PATIENTS

6.3.1 Inclusion Criteria

- *Screening Visit*

Patient fulfilling all of the following criteria will be eligible at Screening Visit:

1.1. Informed consent signed and dated.

1.2. Female or male aged ≥ 18 years old.

1.3. Known DES requiring artificial tears for at least the last 3 months prior to screening visit.

- *Randomisation Visit*

Patient fulfilling all of the following criteria will be eligible at Randomisation Visit:

[redacted]

1.6. Diagnosis of moderate to severe dry eye syndrome defined by OSDI Score ≥ 23.

1.7. Ocular discomfort evaluated by VAS ≥ 40 mm.

[redacted]

[redacted]

6.3.2 Exclusion Criteria

Patient will NOT be eligible if ONE OR MORE of the following criteria is met at both screening and inclusion visits

<u>Ophthalmic Exclusion Criteria in AT LEAST ONE EYE</u> [2.1]

2.1.1 Far 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 Severe 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.

[redacted]

Specific Exclusion Criteria Regarding Childbearing Potential Women [2.3]

2.3.1 Pregnancy or breast-feeding.
2.3.2 Childbearing potential woman neither surgically sterilized nor using an adequate contraception as oral contraceptive, intra-uterine device, subcutaneous contraceptive implant, vaginal ring, patch.

Exclusion Criteria Related to General Conditions [2.4]

2.4.1 Alcohol addiction and heavy smoker according to investigator's judgement.
2.4.2 Inability of patient to understand the investigation procedures or to give informed consent.
2.4.3 Non-compliant patient (e.g., not willing to attend a visit or completing the self-questionnaire; way of life interfering with compliance).
2.4.4 Participation in this investigation at the same time as another clinical investigation/study.
2.4.5 Participation in this investigation within the exclusion period of a previous study/investigation with a minimum of one month.
2.4.6 Patient previously included in this investigation.
2.4.7 Patient being institutionalised because of legal or regulatory order, inmate of psychiatric wards, prison or state institutions, or employee of the investigation sites or of the Sponsor's company.
2.4.8 Patient not covered by the government health care scheme of the country in which he/she is living (if applicable).
2.4.9 Patient under guardianship/ward of court.

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

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

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

Table 7 Prohibited treatments (medications/non-medicinal therapies/procedures)

<table>
<tr><th colspan="5">CONCOMITANT MEDICATIONS/NON-MEDICINAL TREATMENTS NOT ALLOWED BEFORE AND DURING THE INVESTIGATION</th></tr>
<tr><th colspan="3">Before the screening visit
(Before Day 1-10/Day 1-7)</th><th>Run-in period
(From Day 1-10/Day 1-7 to Day 1)</th><th>After inclusion
(Day 1 to Day 36)</th></tr>
<tr><td>12 months</td><td>3 months</td><td>1 month</td><td>Run-in period</td><td>Treatment period</td></tr>
<tr><td colspan="5">Cataract or ocular surgery</td></tr>
<tr><td colspan="5">Isotretinoin, cyclosporine, tacrolimus, sirolimus, pimecrolimus
And others immune-suppressive medications
Topical corticoids and topical antihistaminics</td></tr>
<tr><td colspan="5">Lachrymal plugs</td></tr>
<tr><td colspan="5">Any change in systemic medication</td></tr>
<tr><td colspan="5">Contact lenses</td></tr>
<tr><td colspan="5">Antihistaminic and steroid systemic medication</td></tr>
<tr><td colspan="4">Any ocular medication except Hydrabak®</td><td></td></tr>
<tr><td colspan="4"></td><td>Any ocular medication including artificial tears except IMD</td></tr>
</table>

6.3.3 Criteria and Procedures for Treatment/Investigation Withdrawal or Discontinuation

There are no pre-defined criteria for temporary or permanent treatment discontinuation with the exception of those listed below.

The patient may voluntarily withdraw from the 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 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/(DD necessitating discontinuation from the investigation
- An exceptional circumstance (*e.g.* COVID-19 pandemic).

If a patient is tested COVID-19 positive during the investigation, the patient has to inform the investigator.

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

If a patient prematurely stops the IMD or should/wants to prematurely withdraw from the investigation for any reason, the masked investigator must make every effort to perform all the evaluations described for the premature investigation discontinuation visit/for the final visit (Visit#4) as soon as possible.

The ophthalmologist investigator will prescribe the best appropriate treatment to the patient.

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

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 but are not subsequently randomised 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.

In the case of an **exceptional circumstance (e.g. COVID-19 pandemic)**: **See 6.1.4.4**

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 in different sites in EU or outside EU.

6.3.5 Point of Randomisation

The point of randomisation corresponds to the time at which a patient is assigned with a randomisation number. This randomisation number will be allocated when all Inclusion / Exclusion criteria are verified.

6.3.6 Total Expected Duration of the Clinical Investigation

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

6.3.7 Expected Duration of each Patient's Participation

The treatment period for each patient is 36 + 3 days and a total investigation duration of 49 days (maximum days comprising the run-in, treatment period).

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

It is planned to randomise 250 patients in order to have 226 evaluable patients (113 per group) for the FAS analysis.

Evaluable patients will be defined as randomised patients having received at least one dose of IMD and with at least one performance endpoint post-randomisation visit.

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

The enrolment period is estimated at about12 months.

[redacted]

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 (urine pregnancy testing will be performed at V1 and for other visits, this will be discussed verbally with patients).

See **Section 15**

6.4 PROCEDURES

Timing of procedures is presented in **Table 2**

All procedures will be precisely described in the investigator manual.

All procedures should be performed by the same **masked investigator or delegate for selected tasks** (according to local requirements, the investigator may delegate tasks to collaborator)

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 Characteristics

The following characteristics will be collected:

- Age (in years) and gender,
- Previous and concomitant ocular and non-ocular medications,
- History of the investigated disease
- Ocular medical and surgical history with relevant diagnosis other than the investigated disease
- Systemic medical and surgical history with relevant diagnosis

6.4.1.2. Performance Measures

- *Ocular Surface Disease Index (OSDI) Questionnaire*

The OSDI questionnaire (Schiffman et al., 2000; Miller et al., 2010) must be completed by the patient at the beginning of a 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.

[redacted]

- *Ocular discomfort (VAS)*

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

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

0	100
No discomfort	Maximal discomfort.

- *Soothing sensation*

Patient will be asked : "How would you rate your soothing sensation within 15 minutes after study treatment instillation(s)?

The soothing sensation felt by the patient within 15 min after MD 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 visit post-baseline.

- *Ocular symptoms within the last 48 hours*

Patient will be asked: "How do you judge the severity of your following ocular symptoms within the last 48 hours?"

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

0 = Absent

1 = Mild, present but not disturbing

2 = Moderate, disturbing, but not limiting with daily activities

3 = Severe, very distressing and interfering with daily activities

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

- *Slit Lamp Examination*

- <u>Conjunctival hyperaemia</u>

The level of severity of conjunctival hyperaemia will be scored using the [redacted] photographic scale (0 to 5) in each eye.

[redacted]

- <u>Tear Break-Up Time (TBUT)</u>

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.

- <u>Total ocular surface staining (Oxford scale)</u>

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

[redacted]

The Global Score (sum of score reported for each area: corneal + conjunctival) for each eye will be recorded.

- *Schirmer Test*

The Schirmer test will be performed without anaesthesia.

The test should be done **without touching directly the strip with the finger** to avoid contamination of skin lipids.

The strip should be placed in the temporal part to avoid any contact with the cornea. The patient should keep the eyes closed. Values should be measured just at the end of the 5 minutes.

The Schirmer test will be measured in mm/5 min in each eye.

- *Performance Assessment by the investigator*

The investigator has to answer to the following question at the end of the patient examination:

"Do you consider the IMD performance as:

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory"

- *Patient satisfaction*

✓ Global satisfaction assessment by the patient

The patient has to answer to the questionnaire in local language.

"In a scale from 0 to 10, where 0 is COMPLETELY UNSATISFIED and 10 is COMPLETELY SATISFIED, indicate the number which corresponds the best to your overall satisfaction"

.

✓ Global patient Satisfaction assessment with the use of the bottle

The patient has to answer to this question in local language.

"Are you satisfied with the use of the bottle?"

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory"

6.4.1.3. Safety measures

Adverse Events and device deficiencies 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**.

DD will be also collected.

- Ocular Symptoms Upon Instillation,

The severity of ocular symptoms upon instillation will be assessed by the patient.

"Since the last visit, have you felt any unusual ocular sensation immediately after study treatment instillation (s)?

The following symptoms will be evaluated:

- Burning/Irritation
- Stinging/Eye Pain
- Itching/pruritus
- Eye dryness feeling
- Foreign body sensation
-

Severity will be assessed based on a 4-point scale:

0 = Absent,
1 = Present but not disturbing,
2 = Disturbing
3 = Very disturbing.

The translation of these terms will be provided to the site.

- Visual Acuity

Far (BCVA) will be assessed in each eye using the same chart throughout the study. It can be expressed using units as /10, decimal notation, MAR, logMAR, EDTRS or Snellen notation. It will be analysed after conversion in LogMar. [redacted]).

- Ocular Tolerance Assessment by the investigator

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

"How do you consider the IMD ocular tolerance?

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory"

- Ocular Tolerance Assessment by the Patient

The investigator has to 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"

- Treatment Compliance Evaluation

Patient will return all investigational products (IMDs and Hydrabak®), whether used or unused.

For Hydrabak and IMD *(*T2769 or Vismed® Multi), 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, it will be asked to add the date and hour of last instillation before the beginning of each study 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 on paper patient diary.

** one instillation = 1 drop in each eye*

6.4.1.4. Prior and Concomitant Treatment

At screening visit, the patient will be asked what treatment he/she has taken within the last 3 months; this will be recorded on the Source 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 Source documenting product details, dose and treatment duration.

6.4.1.5. Prohibited Prior and Concomitant Medications or Treatments

Prohibited treatments as well as modifications of prohibited treatments during the investigation are presented in the summary in the exclusion criteria and in **Table 1**

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

Laboratoires THEA through 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 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 CROs in charge of monitoring, prior to the commencement of the study of all relevant chemical, toxicological and clinical information required for the proper planning and conduct of the investigation and will update this as often as may be necessary during the course of the study. 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 study 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.

A run-in period with Hydrabak® is scheduled to have patient with the same treatment at the baseline visit.

6.4.4 Methods for Addressing these Factors in the Clinical Investigation

However, to not compromise the outcome of the clinical investigation, the patient will be randomly assigned to 1 of the 2 treatment groups during the randomisation visit.

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

6.5.1 Source Documents

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

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

Source documents are any original documents, data and records. These may include, but are not limited to, patient medical records, hospital charts if any, clinic charts, laboratory notes, patient's questionnaires, patient's diaries if any, the investigator's 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 paper questionnaire and will be considered as source data:

- Run-in treatment compliance: number of instillations/day
- IMD compliance: number of instillations/day
- OSDI questionnaire
- VAS

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 study 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 DES for each eye

  - Date of onset of the diagnosis in each eye (months/year)
  - Previous use of artificial tears

- Ocular and systemic medical and surgery history (other than 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 screening 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 hyperemia, corneal and conjunctival staining by fluorescein with a yellow filter and TBUT
- Shirmer 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 Run-in treatment dispensation, instruction for use and kit number provided to patient
- Information on IMD dispensation, including kit number assignment with IRT notification
- Run-in treatment compliance collected by reviewing patient's diary and interview and checked against returned kit
- IMD compliance collected by reviewing patient's diary and interview and checked against returned IMD
- Information on used/unused IMD by patient, assessed by unmasked collaborator
- 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 review of source documentation (SDR= Source Data Review) 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 randomised 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 subject in order to confirm that the site is compliant with ICH GCP and the Protocol
- ✓ 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 protocol 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 and to IRT (if applicable).

e-CRF must be completed for each patient screened in the investigation. 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-CRF for this investigation must be consistent with the patients' source documentation (i.e., medical records).

A copy of completed e-CRF pages, SAE / Pregnancy will be stored in the investigator's archives for 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 and breaking the blind 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 dose of IMD and analysed as treated.

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

- **Intent-to-treat (ITT) set:**

All randomised patients and analysed as randomised.

- **Full analysis set (FAS):**

All randomised patients, having received at least one dose of IMD, with at least one baseline and one post-randomisation performance assessment on treatment and analysed as randomised.

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 blind 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 [redacted] endpoints. Patients will be analysed as treated.

7.2 STATISTICAL ANALYSIS

Statistical descriptions will be performed by groups. For disposition and demography description will also be presented overall.

Demographics and baseline characteristics, including history of dry eye, medical/surgical history (by System Organ Class (SOC) and PT separately for ocular and systemic history), previous and concomitant ocular/non-ocular treatments will be summarised by treatment group and overall. Parameters recorded for both eyes will be described separately for the study eye and for the contralateral eye.

[redacted]

[redacted]

Baseline is defined as the assessment at randomisation visit (D1) before the first IMD instillation. Missing value at randomisation visit (D1) will not be replaced.

For endpoints defined as change from baseline, descriptive statistics by visit and the change from baseline will be presented.

The extent of exposure of patients to run-in treatment and to IMD compliance will also be summarized.

Disposition, demographics, baseline characteristics and exposure will be summarized for the FAS, PP set and Safety set [redacted].

7.2.1 Performance Analyses

Primary performance endpoint [redacted] will be primarily analysed on the FAS. Sensitivity analysis of the primary [redacted] endpoints will be performed on the PP.

[redacted]

For primary [redacted] performance variables, descriptions will be given by treatment group at each assessment time. Change from baseline will be also presented, when applicable.

When using inferential analysis, least square (LS) means and its standard errors will be displayed for each treatment group. The LS means for the difference (T2769 - Vismed® Multi) between the treatment groups' change from baseline, its 95% confidence interval (CI) and the superiority p-value, when applicable, will be provided.

Primary [redacted] performance

Objective

The primary objective is to demonstrate the non-inferiority of T2769 compared to Vismed® Multi in terms of total ocular surface staining (Oxford score) after 35 days of treatment [redacted]

Variables

The primary performance variable is change from baseline (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D36 in the study eye. The total ocular surface staining (Oxford score) is defined as the sum of corneal, temporal, and nasal staining scores.

[redacted]

Primary analysis

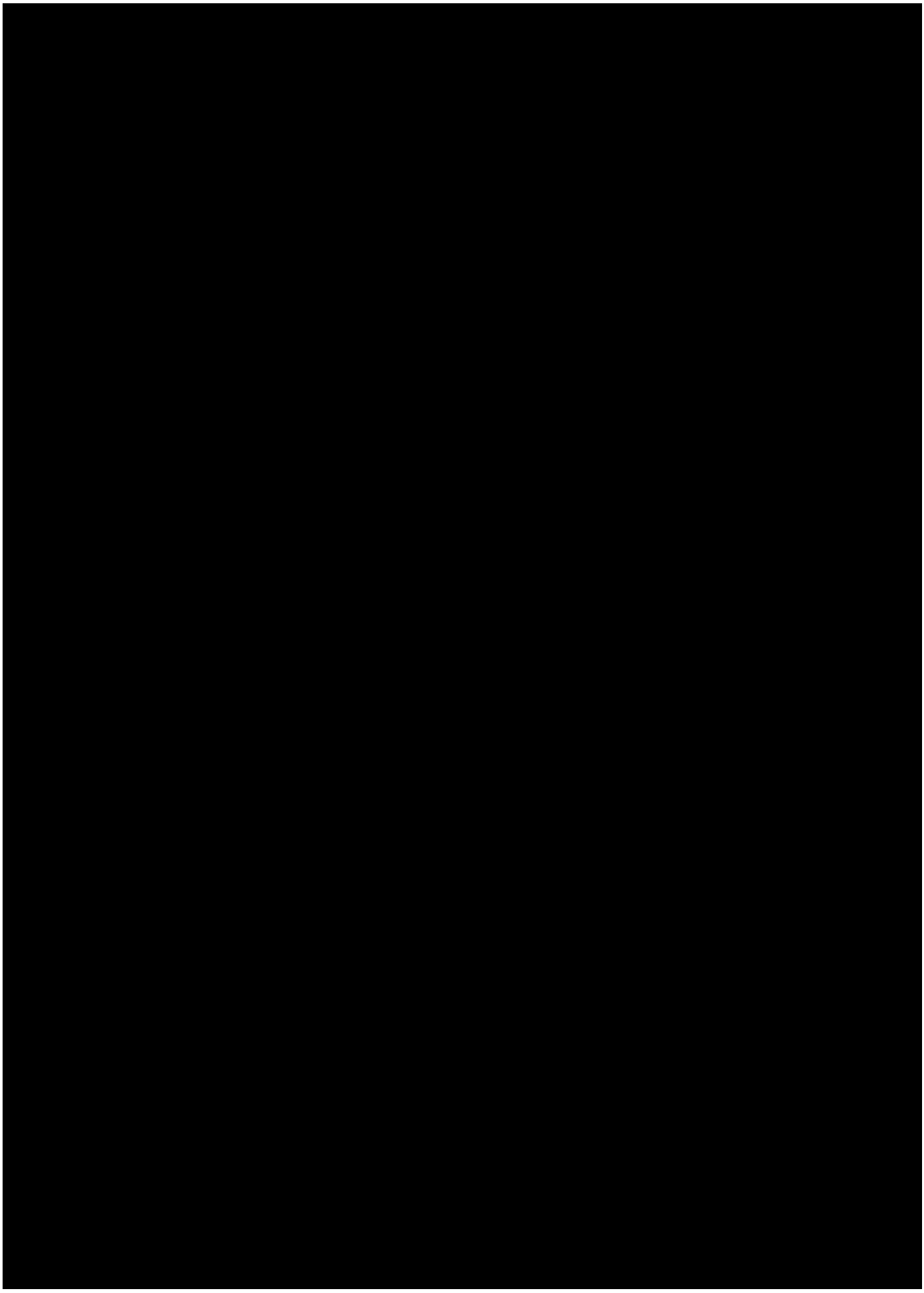
The inferential analyses of the primary performance variable will aim to assess the non-inferiority of T2769 to Vismed® Multi. The hypothesis of non-inferiority of T2769 compared to Vismed® Multi will be tested by calculating the bilateral 95% CI of the difference between groups (T2769 – Vismed® Multi) of the total ocular surface staining (Oxford score) at D36.

The non-inferiority of T2769 to Vismed® Multi on the total ocular surface staining (Oxford score) will be primarily tested using a Mixed Model for Repeated Measures (MMRM) approach. The model will include treatment and scheduled visit time points (D15 and D36) as fixed factors, patient

as random factor, and baseline total ocular surface staining (Oxford score) as continuous covariate. Treatment by scheduled visit time point and baseline total ocular surface staining (Oxford score) by scheduled visit time point will be included as an interaction term in the model. [redacted]

The 95% CI for treatment effect (difference T2769 - Vismed® Multi) will be estimated at D36 in this model. Non-inferiority will be achieved if the upper bound of the 95% CI for the difference between treatment groups (T2769 - Vismed® Multi) is lower than the margin of 2 points.

[redacted]



[redacted]

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 TEAEs.

Ocular and systemic TEAEs will be analysed separately on the basis of the localisation as recorded by the investigator in the CRF.

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 blind review meeting to decide if they have to be considered as TEAE or not.

Separate descriptions of ocular and systemic TEAEs will be performed by treatment group:

- 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 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 AEs, by SOC, PT and severity.
- Number and percentage of patients with AEs, by SOC, PT and relationship with IMD.

Documented list of individual data concerning TEAEs will be performed.

Separated descriptions of ocular and systemic during the run-in period will be performed overall:

- Number and percentage of patients experiencing at least one TEAE, as well as the number of TEAEs, by SOC and PT. The same summary table will be performed for SAEs (if any), and TEAEs related to run-in treatment.

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

List will also be performed on non-TEAEs (before the first IMD instillation).

[redacted]

[redacted]

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.

[redacted]

7.5 SAMPLE SIZE CALCULATION AND JUSTIFICATION

The sample size is driven by the statistical hypotheses on the primary [redacted]

[redacted]

[redacted]

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.

[redacted]

[redacted]

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

No Interim Analysis (IA) is planned.

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

Random allocation of patients in the T2769 group or Vismed ® Multi group will assure that all patient's known and unknown characteristics are similar and balanced between groups at the beginning of the investigation, avoiding the selection bias.

Masking will be achieved by providing each product unit with identical cardboard box and by identifying it by an IMD kit number.

7.10 MANAGEMENT OF POTENTIAL CONFOUNDING FACTORS

Baseline value will be included in all MMRM models (if applicable) as covariate.

Other covariates will be explored and detailed in the SAP.

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

The overall alpha (family-wise error rate) will be maintained at the one-sided α-level of 0.025 by using the following testing strategy: [redacted] to demonstrate that T2769 is non-inferior (according to a pre-defined non-inferiority margin of 2 points in the total Oxford grade) to Vismed® Multi in patients with moderate to severe dry eye syndrome as assessed by the total ocular surface staining grade change from baseline to D36 in the study eye, [redacted]

7.12 SPECIFICATION OF SUBGROUPS

Not applicable.

[redacted]

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.

7.17 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 center 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 and correct and in 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 concomitants 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 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 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 investigation.

In particular, the patients are informed by the investigator during the delivery of the 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 patients, 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. CRO Data Management 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 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 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 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 last device has been placed on the market, to meet the Sponsor regulatory local 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 investigation to ensure that the investigational site is suitable and has the suitable facilities, staff and capacity for the conduct of the 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 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 investigation may be subjected to auditing by representatives of the Sponsor and/or to inspection(s) by authorised 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 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 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 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 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 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 investigation, in case of important deviations observed in an investigational site (such as deviations related to inclusion and/or exclusion criteria, deviations that may put a patient at risk), the Sponsor could decide to stop the enrolment in this site.

At the end of the investigation, CIP deviations will be reviewed and classified as minor or major during a blind data review meeting that will be held before database lock. The exclusion of patients from the analysis sets (see details of analysis sets in **Section 7**) will be discussed during the blind 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 unmasked collaborator 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) and the Drug Accountability Module and Return Form in IWRS.

The masked investigator will remain masked to the IMD. He/she will not retrieve the product from any patient.

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 a depot in the involved country or 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. An import licence to authorize the return from UK to France is mandatory. At receipt, The CRO of packaging and Labelling has to confirm the Good Receipt to the site team and monitor.

All details regarding return of used and unused IMD will be recorded in the Drug accountability return module in IRT.

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

12.STATEMENTS OF COMPLIANCE

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

Prior to commencement of the investigation, the Sponsor or his legal representative in the community must submit a valid application, with the same version of the documentation, to the IEC and the 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 investigation in the last country in which the clinical investigation has been conducted/in accordance with the local regulations.

If the investigation has terminated prematurely, the reason for the termination must be given (see **Section 16**)

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 investigation are governed by the applicable law.

The Sponsor will arrange for patients participating in this 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 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 ISO14155 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 investigation. The measures taken to safeguard the patient's privacy and the protection of personnel data should also be described in the informed consent. The patients must be informed about their right to abstain from participating in the investigation and to withdraw their consent at any time without affecting their medical care.

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

The informed consent must be signed 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 informed consent form (ICF). A witness will be present during the entire informed consent discussion. The witness will personally sign and date the ICF to confirm that the information was accurately explained to the patient, and apparently understood, and that consent was freely given.

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

Serious Adverse Event (SAE): 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
- ✓ 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): ADE that has resulted in any of the consequences characteristic of a serious adverse event .

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

NOTE: Anticipated SADE (ASADE): 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

     o the investigational device or procedures are applied to;

     o 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 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 [redacted] will have to be completed, dated and signed by the investigator and send by email [redacted] or by fax [redacted]

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 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 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 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** [redacted].

Laboratoires THÉA must

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

- report to regulatory authorities/EC/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, the 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 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 investigation the investigator must:

- Report immediately (maximum 24 hours) the pregnancy status to Laboratoires THÉA using the email [redacted]
- 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.

15. VULNERABLE POPULATION

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

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

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 patient.
- 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 with the reason(s) for the suspension, as per the applicable regulatory requirement(s).

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 patient
- 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 patient.

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

Should the 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 investigation had been completed.

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

- Occurrence of
  - new events related to the conduct of a investigation or the development of an IMD likely to affect the safety of patient, such as:
    - a SAE which could be associated with the investigation procedures, and which could modify the conduct of the 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 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 investigation.
- If Laboratoires THÉA should wish to discontinue the investigation for commercial reasons.
- If Laboratoires THÉA had reasons to believe that the investigation could not be satisfactorily completed, including, but not limited to, the reason that inadequate numbers of patient could be enrolled or insufficient centres 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 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 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 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 patient 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 investigation, the investigator must perform at least one premature discontinuation visit following 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.

The role of investigator-masked and Unmasked collaborator will be the same as previous visits.

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 person (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 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 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 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.