CLINICAL STUDY PROTOCOL

Study No. LT4090-201

IND-156259

Sponsor

Laboratoires THÉA

[redacted]

Phone: [redacted]

Date of the initial Clinical Study Protocol: **17 April 2024**

Version of the initial Clinical Study Protocol: 2.0

TITLE: *Efficacy and safety assessment of T4090 ophthalmic solution (preservative-free Kinezodianone R HCl 0.2% or 0.3%) versus Rhopressa® ophthalmic solution (preserved netarsudil 0.02%) in patients with open-angle glaucoma or ocular hypertension*

LABORATOIRES THÉA

Clinical Study Protocol (CSP) No.:	LT4090-201
Investigational Medicinal Product (IMP):	T4090
Indication:	Open Angle Glaucoma or Ocular Hypertension
Study Phase:	II
Coordinating Investigator	[redacted]
Sponsor's Medical Expert	[redacted]

STATEMENT OF THE SPONSOR

Efficacy and safety assessment of T4090 ophthalmic solution (preservative-free Kinezodianone R HCl 0.2% or 0.3%) versus Rhopressa® ophthalmic solution (preserved netarsudil 0.02%) in patients with open-angle glaucoma or ocular hypertension

The information contains in this CSP is consistent with:

- The current risk-benefit evaluation of the investigational medicinal product (IMP)
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of Good Clinical Practice as described in the International Council for Harmonisation (ICH) Guidelines, ICH E6 (R2) and FDA regulation.

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

SPONSOR: LABORATOIRES THÉA

Clinical Affairs Director

[redacted] 17-avr.-24 [redacted]

First Name - Name *date* *signature*

Medical Development Director

[redacted] **MD** 22-avr.-24 [redacted]

First Name - Name *date* *signature*

Biometrics Manager

[redacted] 22-avr.-24 [redacted]

First Name - Name *date* *signature*

INVESTIGATOR SIGNATURE PAGE

Efficacy and safety assessment of T4090 ophthalmic solution (preservative-free Kinezodianone R HCl 0.2% or 0.3%) versus Rhopressa® ophthalmic solution (preserved netarsudil 0.02%) in patients with open-angle glaucoma or ocular hypertension

The signature below:

- Confirms my agreement to conduct the study in compliance with Good Clinical Practices (GCP), applicable laws and regulations, and the clinical study protocol 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 study essential documents in the Investigator Study File (ISF) until Laboratoires THÉA informs me these documents are no longer needed (e.g., over *25* years).
- Ensure that all persons assisting with the study are adequately informed about protocol, the IMP(s) and their study-related duties and functions.
- Confirms that I have read this protocol and I agree to comply with all parts or items.

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

STUDY SITE

Principal Investigator

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

SPONSOR: LABORATOIRES THÉA

Clinical Project Leader

[redacted]	19-avr.-24	_____ [redacted]
First Name - Name	*date*	*signature*

CONTACTS PAGE FOR THE STUDY

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[redacted] Biometrics Manager	Email: [redacted]
[redacted] Global Safety Manager [redacted] Safety & Med info Specialist	Email: [redacted]
[redacted] Clinical Project Leader	Email: [redacted]
IMP Complaints	Email : [redacted]
All details regarding the CRO for monitoring will be presented in the ISF.	

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AH	Aqueous humor
[redacted]	[redacted]
ATC	Anatomic Therapeutic Chemical
BAK	Benzalkonium Chloride
BCVA	Best Corrected Visual Acuity
CEC	Corneal endothelial cells
C/D	Cup of Disc
CFS	Corneal Fluorescein Staining
CI	Confidence Interval
[redacted]	[redacted]
CRF	Case Report Form
CRO	Contract Research Organisation
Db	Decibel
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture system
EMA (ex-EMEA)	European Medicines Agency
FAS	Full-Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
IAC	IridoCorneal Angle
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Study File
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
LS	Least Squares
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MD	Mean Deviation
MDC	Multiple-dose container
MMRM	Mixed Model for Repeated Measures
[redacted]	[redacted]
[redacted]	[redacted]
NO	Nitric Oxide
NSAIDs	NonSteroidal Anti-Inflammatory Drugs
OAG	Open-angle glaucoma

OHT	Ocular hypertension
PF	Preservative-Free
PGA	Prostaglandin analogue
POAG	Primary Open angle Glaucoma
PP	Per Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
ROCKi	Rho-kinae inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDC	Single Dose Container
SDV	Source Data Verification
SOC	System Organ Class
SLT	Selective Laser Trabeculoplasty
SPK	Superficial Punctuate Keratitis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGL	TriGlyceride Lipase
TEAE	Treatment Emergent Adverse Event
TM	Trabecular meshwork
USA	United States of America
YAG	Yttrium Aluminum Garnet

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2 STUDY OBJECTIVES AND PURPOSE

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to compare the ocular hypotensive efficacy of two concentrations of T4090 (Kinezodianone R HCl 0.2 % and 0.3 %) ophthalmic solution with Rhopressa ophthalmic solution.

[redacted]

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 OVERVIEW

This is a phase II, multicenter, randomized, investigator-masked, 3-parallel groups, 7-week treatment duration in patients with OAG or OHT.

In this study approximately 126 patients (naïve patients or using ocular hypotensive medication) will be randomized.

The study duration will be 12 weeks.

A minimum of 4 visits and a maximum of 7 visits are planned. The number of visits will depend on the patient's screening status (naïve patients or patients using ocular hypotensive medication).

Randomized patients will attend 3 visits at the investigator center during the study treatment period:

- Visit #1: Screening visit:

At the end of the Screening visit:

- An eligible patient without ocular hypotensive medication (naïve patient) is randomized.
- An eligible patient using ocular hypotensive medication will undergo a washout period.

During the washout period, the patient may attend the following visits:

- Visit #1.1: Optional visit planned according to the investigator´s judgement at any time during the washout period for intraocular pressure (IOP) monitoring
- Visit #1.2: Visit in case of extension of the washout period. If the IOP meets the entry requirement, visit is directly recorded as the Randomization visit (Visit #2 – D1).

- Visit #2 – D1: Randomization visit (Day 1)
  - For naïve patient this is the same day as Screening visit or in the 2 following weeks when the patient's eligibility is confirmed
  - For patient using a hypotensive medication before Screening visit, this is the day after the end of the washout period (with extension or not)

Only a patient screen failed at Visit #1 may be rescreened (1 time) with a new attributed patient number.

- Visit #3 – Week 2 (W2) - Day 15 (±2 days)
- Visit #4 – Week 4 (W4) - Day 29 (±3 days)
- Visit #5 – Week 7 (W7) - End of treatment visit, Day 50 (±3 days)

The investigator prescribes to the patient the best appropriate antiglaucoma treatment at the end of the Visit#5.

In case of premature study treatment discontinuation, the investigator prescribes to the patient the best appropriate antiglaucoma treatment and a visit should be scheduled as soon as possible and recorded in premature study treatment discontinuation visit.

Then the patient must perform all visits and study procedures planned until the Visit #5 (W7 visit).

Figure 1. Overall design of the study (*pretreated patient*)

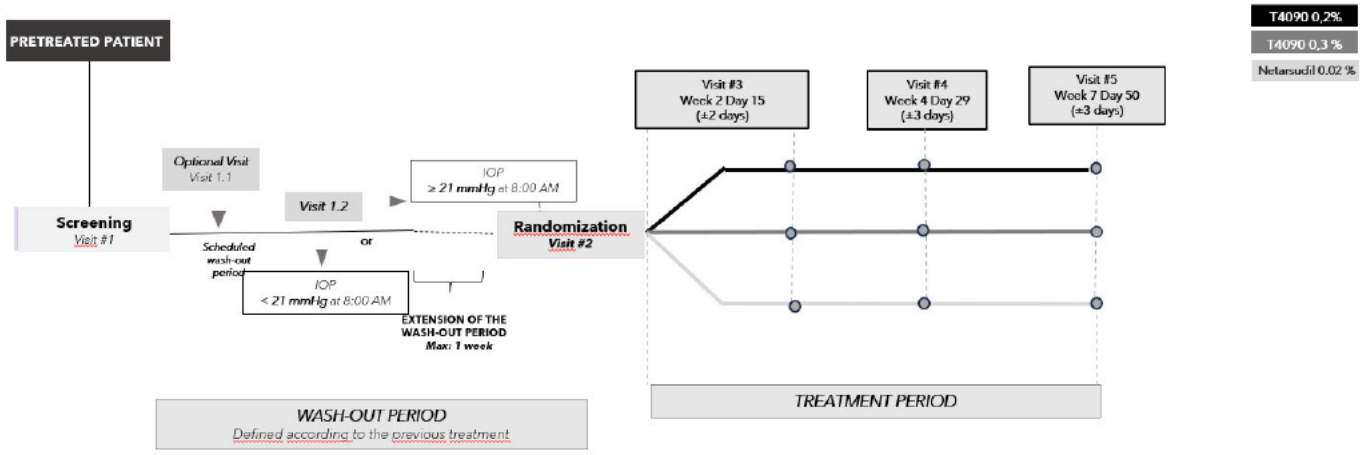
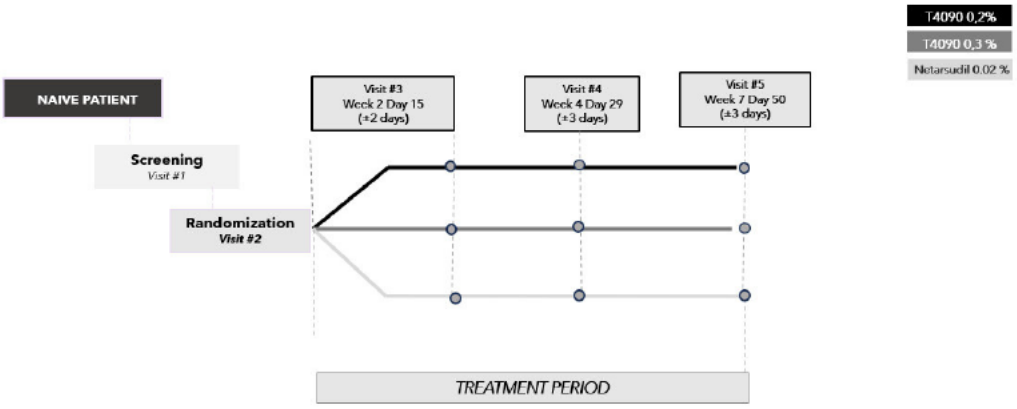


Figure 2. Overall design of the study (*naïve patient)*



3.1.1 Wash-out for pre-treated patients

Patients must be able to safely discontinue their current antiglaucoma treatment for the specified washout period prior to Visit #2 (D1) in order to determine their IOP eligibility.

The predefined washout period is based on the patient's previous treatment type from 5 days to 28 days[a] as follows:

[a] If the baseline IOP does not meet the study entry criteria, the investigator can decide to extend the washout period for a maximum 1 week additional (e.g., 28 days+7 days). See below for further details

The washout period begins the first day without treatment:

- If the last instillation of ocular hypotensive medication is performed the day before the Screening visit, the washout period will start the day of the Screening visit.
- If the last instillation of ocular hypotensive medication is performed on the morning of the Screening visit, the washout period will start the day after the Screening visit.

The end date of the washout period is the day before the Randomization visit.

During the washout period, an optional visit might be planned according to the investigator´s judgement at any time for IOP monitoring. This visit will be considered as visit #1.1.

At the end of the washout period defined according to the previous treatment, patients will visit the investigators site and have their IOP measurement taken at 8:00 AM.

- If the investigator considers that the IOP does not meet the entry requirement, the visit is recorded as Visit #1.2, and the washout period can be extended up to a maximum of 7 days if the investigator considers it safe to do so. If the washout is extended, the maximum washout will then be 13 to 38 days (depending on the previous treatment).
- If the IOP meets the entry requirement, the visit is directly recorded as the Randomization visit (Visit #2 – D1).

3.1.2 Treatment Period

The 7-week treatment period will follow the washout period. It will last from the Randomization visit (D1; Visit #2) to the W7 - End of treatment visit, Day 50 (±3 Days).

The patient will attend the site for the study visits at W2 (Day 15±2 days; Visit #3), W4 (Day 29±3 days; Visit #4) and W7 (Day 50±3 days; Visit #5) for assessment of efficacy and safety.

At the Randomization visit (D1; Visit #2), if the patient meets the eligibility criteria, she/he will be randomly assigned to one of the following 3 treatment arms:

Test product:

- T4090 (PF Kinezodianone R HCl 0.2%) ophthalmic solution, in single-dose container (SDC)
- T4090 (PF Kinezodianone R HCl 0.3%) ophthalmic solution, in SDC.

Reference product:

- Rhopressa (preserved netarsudil 0.02%) ophthalmic solution, in multiple-dose container (MDC).

The patient will administer the assigned treatment (T4090 0.2% or T4090 0.3% or Rhopressa) once daily at 8:00 PM (±1 hour) in the conjunctival cul-de-sac of each eye from D1 to the day before the End of treatment visit (W7 – Visit #5 – Day 50 (±3 days)).

For randomized patient, in case of **study treatment premature discontinuation**, a premature study treatment discontinuation visit should be scheduled as soon as possible. Then the patient must perform all planned visits and study procedures planned until the Visit #5.

3.2 JUSTIFICATION OF THE STUDY DESIGN

This is a Phase II study. The clinical data obtained will be used to design a large Phase III clinical study.

Multicenter study:

Twenty to 30 sites (USA) are planned in this study. A multicenter design has been chosen to achieve patients' recruitment within the study timelines.

Randomized:

At the Randomization visit on D1 (Visit #2), patients who meet all eligible criteria will be randomly assigned to one of the 3 treatment groups. Randomization keeps the investigators masked from the treatment given to the patient and is considered the most reliable method for evaluating the effects of interventions in an unbiased manner.

Investigator-masked:

A double-masked study design was not feasible due to the different packaging between T4090 and Rhopressa (SDC *versus* MDC).

To obtain unbiased data, investigator-masked study is designed, meaning that the masked investigator or masked authorized collaborator, in charge of ophthalmic examinations are not aware of the allocated treatment.

To respect this constraint, the following precautions will be taken:

- **Masked and unmasked teams** will be assigned. The role and responsibilities of masked and unmasked site staff will be further described in the Study Personnel Delegation Form. The same masked investigator must attend all study visits from randomization visit to the last visit for the same patient.

During the whole study treatment period the **masked investigator** or **other masked qualified site staff** per local regulation (=**designee),** in charge of ophthalmic examinations (including IOP measurement) will not be aware of the allocated treatment (T4090 or Rhopressa). He/she will not deliver, nor receive the returned medication from the patient and will be trained not to discuss IMP with patients.

- IOP measurements will be performed by two persons: the **masked Investigator/designee** (same for all visits from Randomization visit onwards) reaches the correct applanation effect in the slit lamp and **must be masked to the readout** of the tonometer during the measurements. A second staff member reads and transcribes the IOP values (readout of the

tonometer) into the patient source document once the masked Investigator/designee reaches the correct applanation effect in the slit lamp.

- Each site must have at least one **unmasked team member** dedicated to IMP management (e.g. Unmasked Investigator and /or Pharmacist or other qualified site staff/designee per local regulation). This **unmasked team member** does not participate in the evaluation of patients, after first IMP dispensation and does not communicate any unmasking information with the masked teams.

- Final packaging of IMP will be identical in external appearance to respect the masking: same final packaging, same weight, and dividers to avoid boxes or aluminum pouches to move.
- Instructions will be given to the patient in the informed consent form (ICF)/patient's brochure that she/he must not return used/unused IMP to masked investigator/designee.

At the end of the IMP masking period, the masked investigator/ designee should confirm in the e-CRF that she/he has not been unmasked during the study.

The Sponsor and CRO collaborators responsible for the data medical evaluation will remain masked.

See Section 5.1.4 for details regarding masking and code breaking.

Choice of the control group:

T4090 0.2% or T4090 0.3% are compared with Rhopressa.

[redacted]

[redacted]

Choice of primary endpoint:

The primary efficacy endpoint is the change from baseline (D1) at W7 in the mean diurnal IOP in the study eye. IOP diurnal variations can be substantial and are larger in glaucoma patients than in healthy individuals. Multiple diurnal measurements are necessary for better characterizing the IOP-lowering effect of eye drops and are highly recommended. Measurement will be done at three timepoints: 8:00 AM, 10:00 AM and 4:00 PM)

This Phase II study is designed in order to provide a useful basis for a well-powered pivotal Phase III study assessing efficacy of T4090 in ocular hypertensive or glaucomatous patients.

3.3 ENDPOINTS

3.3.1 Efficacy Endpoints

The primary efficacy endpoint is the change from baseline (D1) at W7 in the mean diurnal IOP in the study eye.

[redacted]

3.3.2 Safety Endpoints

The following safety and tolerability endpoints will be assessed:

- Ocular treatment-emergent AE (TEAE), serious TEAE, IMP-related TEAEs, TEAEs leading to premature study drug discontinuation by system organ class (SOC) and preferred term (PT)
- Systemic TEAE, serious TEAE, IMP-related TEAEs, TEAEs leading to premature study drug discontinuation by SOC and PT
- [redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

4 SELECTION OF PATIENTS

4.1 NUMBER OF PATIENTS

In this study, approximately 126 patients are planned to be randomized to have 120 evaluable patients (3 groups of 40 patients; see Section 7.5).

Evaluable patients will be defined as randomized patients having received at least one dose of IMP and with at least IOP measurements at the three timepoints (8:00 AM, 10:00 AM AND 4:00 PM) for one visit after randomization.

4.2 INCLUSION CRITERIA

Patient fulfilling all the following criteria will be eligible:

1.1. Informed consent signed and dated.*

*Obtained prior to the initiation of any study-related procedures

At the Screening visit:

1.2. Patient (male or female) ≥18 years old

1.3. Patient with OAG or OHT in both eyes**

4.3 EXCLUSION CRITERIA

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

2.1. Ophthalmic Exclusion Criteria in AT LEAST ONE EYE

Patient experiencing at screening visit or having experienced:

2.1.1. Secondary OAG (ex. Pseudoexfoliation, Pigmentary glaucoma)

[redacted]

Patient experiencing at Screening or Randomization visits or having experienced:

2.1.7. History of ocular trauma, eye infection, or/and ocular clinically significant inflammation within the 6 previous months.

[redacted]

2.2. Systemic/non-Ophthalmic Exclusion Criteria

Patient having experienced or experiencing at Screening or Randomization:

2.2.1. Known or suspected hypersensitivity to one of the components of the IMPs or other product used in the clinical study (e.g., fluorescein, lissamine green and topical anesthetic)

[redacted]

2.5 Exclusion Criteria Related to Previous and Concomitant Treatments (Medications/Non-Medicinal Therapies/Procedures)

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

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

Table 3: Prohibited treatments (medications/non-medicinal therapies/procedures) in any eye

Before the Visit #1 – Screening visit				After the Screening visit and during the study (from Visit #1 – Screening visit to Visit #5)
At any time	6 months	3 months	1 month	
Any ocular surgery (other than cataract surgery), previous glaucoma intraocular surgery, refractive surgery or laser treatment (other than Selective Laser Trabeculoplasty [SLT])……..				
	Laser procedure for glaucoma *(SLT)* …….			
	Intra-ocular injection ……..…….……..			
	Anterior Chamber Implant……			
		Cataract surgery……		
			Yttrium aluminum garnet (YAG) laser capsulotomy…….	
			Monoamine Oxidase Inhibitor treatments……	
			Floctafenine, sultopride, amiodarone, quinidine, fluoxetine, paroxetine .	
			Any change in dose regimen for systemic treatments which can have a substantial effect on IOP: • Beta-adrenergic blocking agents • Beta-adrenergic agonist agents • Alpha agonists agents • Alpha blocking agents • Angiotensin converting enzyme inhibitors • Angiotensin II inhibitors • Calcium channel blockers • Diuretics • Nonsteroidal anti-inflammatory agents*	
			Topical ocular steroids and/ or topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs) ……	
				Systemic immunosuppressive, Corticosteroids……..
				Systemic or ocular antiglaucoma treatments…….
				Any other topical ocular treatments (except preservative-free lachrymal substitutes started at least 1 month before the screening visit stable during the study) ……
				Contact lenses wear…… ……

*Short treatment course until 3 days of systemic nonsteroidal anti-inflammatory treatments will be authorised

4.4 STUDY TREATMENT DISCONTINUATION / STUDY DISCONTINUATION

4.4.1 Permanent discontinuation with IMP

Permanent treatment discontinuation is any IMP discontinuation associated with the definitive decision from the investigator or the patient not to re-expose the patient to the IMP at any time.

4.4.2 List of criteria for permanent study treatment discontinuation

The patient may discontinue study treatment under the following circumstances but will continue to be assessed and followed in the study unless the patient refuses:

- The patients may voluntarily withdraw from study treatment if they decide to do so, at any time without penalty and for any reason without prejudice to their future medical care (Declaration of Helsinki).
- if, in the investigator's opinion, there is any situation or condition which puts the patient at significant risk, especially in case of:
  - Any safety reason(s)/AE(s) necessitating the IMP discontinuation
  - Lack of efficacy: if the patient or the investigator does not feel that the IMP has sufficiently controlled the pathology.
  - Intolerance to IMP
  - Patient's non-compliance
  - An exceptional circumstance (unexpected crisis such as the COVID-19 pandemic).

4.4.3 Handling of patients after permanent study treatment discontinuation

In the case of study treatment discontinuation, the investigator will prescribe the patient the best appropriate treatment if needed.

After study treatment is discontinued, the patient should perform the premature study treatment discontinuation visit as soon as possible. Then the patient must perform all planned visits and study procedures until the Visit #5 (W7 visit).

In all cases, the reason(s) and date of study treatment discontinuation must be recorded on the electronic case report form (e-CRF (End of treatment form) and patient files (source documentation). The patient must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 6.2.3.1.

In the case of study treatment discontinuation, the investigator will prescribe the patient the best appropriate treatment if needed.

The patient discontinued for AE(s) will be followed up after discontinuation until the event is resolved or considered medically stable by the investigator.

Randomized participant who premature discontinue the study treatment must not be reincluded.

4.4.4 Procedure and consequence for patient withdrawal from study

The participant may voluntarily refuse to participate in the clinical study or withdraw from the study, at any time without penalty and for any reason without prejudice to his/her future medical care (Declaration of Helsinki).

However, if the participant has been dosed with the IMP, investigation site staff will remind the participant of the risks of leaving the study prematurely.

Site staff will also recommend that the participant remains in contact with the site, and the investigational site should make every effort to inform the participant on the importance of returning for premature study treatment discontinuation visit and to return used/ unused study medication.

Participant withdrawn from the study must not be reincluded.

In every case, the e-CRF must be filled in up to the last visit performed and the primary reason for withdrawal must be recorded on the electronic case report form (e-CRF) (End of study form) and participant files (source documentation).

Participant withdrawn for AE(s) will be followed-up after discontinuation until the event is resolved or considered medically stable by the investigator.

Participant withdrawn from the study must not be reincluded.

4.4.4.1 Lost to follow-up

For a patient who fails to return to the site (patient lost to follow up), the investigator must do his/her best to contact him/her initially by phone, then by letter, and finally by certified mail to obtain the reason of the study withdrawal, to follow any ongoing AE, as specified in this protocol, and to ask the patient to return the used and unused IMP or to organize the pickup of the IMP directly from the patient (according the local regulatory requirements). If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general physician. The evidence of these contacts must be recorded in the patient files.

In every case, the e-CRF must be filled in up to the last visit performed and the primary reason for withdrawal must be recorded on the e-CRF (End of study form) and participant files (source documentation).

4.4.4.2 Screen failure

Screen failure patients are defined as patients who consent to participate in the clinical study and are not subsequently randomized in the study.

If a patient is screen failure at the Visit #1, the reason of screen-failure must be documented in the e-CRF (Status form).

If a patient is screen failure after the Visit #1 (during the washout period, or at Visit #1.1, Visit #1.2), the reason of screen-failure must be documented in the e-CRF (End of study form).

If a patient is screen failure at Visit #2 the reason of screen-failure must be documented in the e-CRF.

In all cases, the information will be recorded in the patient's files and the investigator ensures the continuity of antiglaucoma medication as per routine clinical practice.

4.5 PATIENT IDENTIFICATION AND RANDOMIZATION

Randomization will occur at the Randomization visit (Visit #2 – D1) after all screening and randomization procedures have been performed and eligibility for the study confirmed. The patient who meets the eligibility criteria will be randomly assigned to a treatment group and associated to a randomization number.

The randomization code list stratified by baseline IOP at 8:00 AM in class [redacted]) is generated by the IRT providers.

Patients will be randomized on a 1:1:1 basis to T4090 0.2%, T4090 0.3% or Rhopressa, respectively. The IMP will be allocated to the patients according to randomization using an interactive response system (IRT).

The IMP number should be recorded in all patient source documents and in the e-CRF.

Randomized patient who terminates their study participation for any reason, regardless of whether IMP was taken or not, will retain their randomization number.

See Section 5.1.4 for details regarding masking and code breaking.

5 STUDY TREATMENTS

5.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The patient will be trained for the correct instillation technique of IMP by the **unmasked team member**. The patient will be provided with a patient's study guide.

5.1.1 Test Product: T4090

The IMP T4090 is a PF eye drops solution presented in SDC filled to 0.2 mL. T4090 0.2% and 0.3% solutions are prepared according to the formula's details in investigator's brochure.

Component	Formula (g/100 mL)		Function(s)	Reference to standards
	T4090 0.2%	T4090 0.3%		
Kinezodianone *R* hydrochloride	[redacted]	[redacted]	Drug substance	Internal Method

A single dose contains enough eye drop solution to treat both eyes. For single use only.

The excipients of the T4090 eye-drops [redacted]

Batch number and retest dates will be provided in the certificate of analysis.

5.1.2 Control Product: Rhopressa

Rhopressa (0.02% netarsudil) ophthalmic solution is supplied sterile in opaque white low density polyethylene MDC and tips with white polypropylene caps in 2.5 mL fill in a 4 mL container.

RHOPRESSA	Formula (mg / mL)
Active ingredient Netarsudil dimesylate	0.2
Benzalkonium chloride Boric acid, Mannitol, Sodium hydroxide	0.015%

Batch number and expiration dates will be provided.

5.1.3 Packaging, Labelling and Storage

T4090 will be manufactured by Unither Coutances ([redacted]) in accordance with the European Union (EU) Good Manufacturing Practices (GMP), including the EU GMP Annex 13.

Rhopressa will be obtained from commercial batches.

The IMPs will be packaged by approved contractor in accordance with GMP. The IMPs will be prepared according to a packaging list.

The IMPs will be prepared according to the randomization list provided by the statistician.

5.1.3.1 Packaging

Each treatment unit, *i.e.*, the complete treatment for one patient and for the complete study duration will be as following.

Packaging	**T4090 0.2% 0.3%**	**Rhopressa**	**T4090 0.2% 0.3%**	**Rhopressa**	**T4090 0.2% 0.3%**	**Rhopressa**
	Day 1 to Week 2		Week 2 to Week 4		Week 4 to Week 7	
Primary	20 SDC	1 MDC	20 SDC	1 MDC	30 SDC	2 MDC
Secondary	2 aluminum pouches	1 final cardboard carton	2 aluminum pouches	1 final cardboard carton	3 aluminum pouches	1 final cardboard carton
Tertiary	1 final cardboard carton		1 final cardboard carton		1 final cardboard carton	

MDC=multiple-dose container; SDC=single-dose container

5.1.3.2 Labelling

All labels will be written in the local language. The content of the labelling is in accordance with specifications, regulations, and local requirements (21 CFR312 for US).

Each SDC/MDC/aluminum pouch/ cardboard carton will carry one label.

The cardboard carton will also carry a detachable label (flag label) bearing at least the protocol number and IMP number. This label will be torn off by the person dispensing the IMP to the patient and will be stuck in the patient unmasked source document to record the dispensing procedure.

5.1.3.3 Storage

T4090

T4090 must be stored in the original packaging (aluminum pouches), protected from light in carboard carton at [redacted] and should not be used after the expiry date indicated on the outer cardboard box.

Rhopressa

Rhopressa must be store at 2°C to 8°C (36°F to 46°F) until opening.

After opening, the product may be kept at 2°C to 25°C (36°F to 77°F) for up to 6 weeks.

If after opening, the product is kept refrigerated at 2°C to 8°C (36°F to 46°F), then the product can be used until the expiration date stamped on the MDC. During shipment, the MDC may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

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

If significant changes and/or update on labelling, handling and storage are required during the study, the corresponding sections will be updated by notifying or submitting to Competent Authorities concerned

accordingly. All investigator 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 8.7). In any way, the reasons and the procedures for any changes will be justified and described by the Sponsor.

5.1.4 Masking and Code Breaking

This will be an investigator-masked clinical study. To respect this constraint, a masked and unmasked teams will be assigned. The role and responsibilities of masked and unmasked site staff will be further described in the delegation of function log.

Masking

The **masked investigator/designee**, in charge of ophthalmic examinations (including IOP measurement) are not aware of the allocated treatment (T4090 or Rhopressa).

At the end of the IMP masking period, the masked investigator will confirm in the e-CRF that she/he has not been unmasked during the study.

Each site must have at least one **unmasked team member** dedicated to IMP management (e.g., Unmasked Investigator and /or Pharmacist or other qualified site staff per local regulation).

Only **unmasked team members** are permitted to manage IMP once received on site from Depot. The study IMP must be stored in a secure location.

The IMP will be delivered by the **unmasked team member.**

The **unmasked team member** will explain to the patient how to use the IMP and how to complete the patient daily diary.

This **unmasked team member** does not participate in the evaluation of patients (ophthalmic examinations, including IOP measurement), after first IMP dispensation and does not communicate any unmasking information with the masked teams.

The IMP will be returned by the patient to the **unmasked team member.**

The **unmasked team member** will be in charge for verifying compliance by checking IMP returns, the patient's diary information and by patient's interview. Information regarding compliance will be shared with the **masked investigator/designee** employing a masked approach (*i.e.,* without revealing treatment allocation or type of IP). The unmasked staff cannot help for any blinded procedures such as EDC entry.

Patients will be instructed not to discuss IMP with the **masked investigator/designee**.

All documents that could contain unmasking information must be kept separate from the masked site staff.

Masking will be achieved by providing each product unit with identical cardboard carton (same final packaging, same weight, and dividers to avoid boxes or aluminum pouch to move) and by identifying it by an IMP number.

Code breaking

The code should not be broken except:

- in case of medical emergency (where knowledge of the IMP received would affect the treatment of the emergency)
- or when it is a regulatory requirement (e.g., for Suspected Unexpected Serious Adverse Reactions [SUSARs]).

The masked investigator/designee is responsible for accessing the IRT System to obtain the identity of the IMP received by the patient. If an emergency code breaking becomes necessary, the investigator should notify the Sponsor, if possible, prior to breaking the code.

When a code is broken, the date, time and reason must be recorded in the IRT as well as in the patient's source documentation, and in any associated AE report. The identity of the IMP **should not be** disclosed in these documents.

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

The Sponsor's collaborators responsible for the data medical evaluation will remain masked.

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

5.1.5 Dispensing and Return

5.1.5.1 Dispensing

The IMPs must be dispensed only to patient in accordance with the protocol and the randomization.

At the Randomization visit (D1), once selection criteria have been checked and once the patient is eligible, the randomization will be performed, and an IMP number will be allocated to the patient.

IMP will be delivered by the **unmasked team member**. Each IMP dispensation will be recorded in the related unmasked documentation.

During the whole study treatment period, the **masked investigator** will remain masked to the IMP (T4090 or Rhopressa). He/she will not deliver or receive the returned medication from the patient and will be trained not to discuss IMP with patients.

All information regarding the usage of the IMPs will be given to patients and will be explained by the **unmasked investigator**.

During the study, three deliveries will be performed as follow:

- At Randomization visit (D1): one box containing enough medication for the treatment period D1 to W2 with the daily diary associated to this period will be provided to the patient by the **unmasked team member** with the number assigned by the IRT
- Visit #3 – W2: resupply of one box containing enough medication for the treatment period W2 to W4 with the daily diary associated to this period, will be provided to the patient by the **unmasked team member** with the number assigned by the IRT
- At Visit #4 - W4: resupply of one box containing enough medication for the treatment period W7 with the daily diary associated to this period, will be provided to the patient by the **unmasked team member** with the number assigned by the IRT.

A record of the IMP dispensed to the patient will be maintained by the **unmasked team member** in the patient unmasked medical records and the accountability log.

The **unmasked team member** will instruct patients not to discuss IMP with the **masked investigator** and on method of instilling the doses:

- Treatment period: IMP (T4090 or Rhopressa) will be instilled by the patient one drop in each eye once daily at 8:00 PM (±1 h).

This is crucial to maintain the blind and avoid any accidental unmasking.

5.1.5.2 Return

Patient will return used and unused IMPs in the original packaging and the diaries to the site at each visit (Visit #3, Visit #4 and Visit #5).

The **unmasked team member** counts the number of IMP remaining in the returned pack, completes and validates the accountability log (used, not used, not returned IMP). In addition to returned IMP, he/she questions the patient on the IMP compliance (number of missing doses, if any, modification of instillation time) compares with the information reported by the patient in the daily diary and records the details in the unmasked file.

The **masked investigator will remain masked to the IMP (**T4090 or Rhopressa**). He/she will not deliver and retrieve the product to any patient** and is not allowed to see the IMP documentation (acknowledgement of receipt product, accountability log). All IMP and IMP documents should be stored in a secured locked area.

All study products will be retained for reconciliation by the unmasked study monitor. The unmasked monitor will, upon completion and validation of drug accountability, returned IMP to depot as instructed by Laboratoires THÉA.

5.2 PRIOR AND CONCOMITANT MEDICATIONS

Previous and concomitant treatments have to be recorded on the patient medical record and on the e-CRF documenting product details, dose regimen and intake dates. Concomitant treatment means any medications or non-medicinal therapies given concurrently with the IMP. Any other local or systemic treatment necessary for the patient's welfare has also to be recorded on the patient medical record and on the e-CRF documenting product details, dose, and treatment duration.

5.2.1 Prohibited Prior and Concomitant Medications or Treatments

5.2.1.1 Prohibited Treatments

Prohibited treatments as well as prohibited modifications during the study are presented in the summary in the exclusion criteria and are further detailed in this section.

The prohibited treatments (or prohibited modifications of a treatment regimen) and their periods of use prohibition are listed Table 3.

6 STUDY CONDUCT

Preliminary remark: Informed consent

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

Written informed consent must be obtained prior to initiation of any study procedures or any discontinuation of current medication.

No measures whatsoever described in the study protocol shall be undertaken without such consent indicating that the patient has been given both verbal and written information about the study and the IMP.

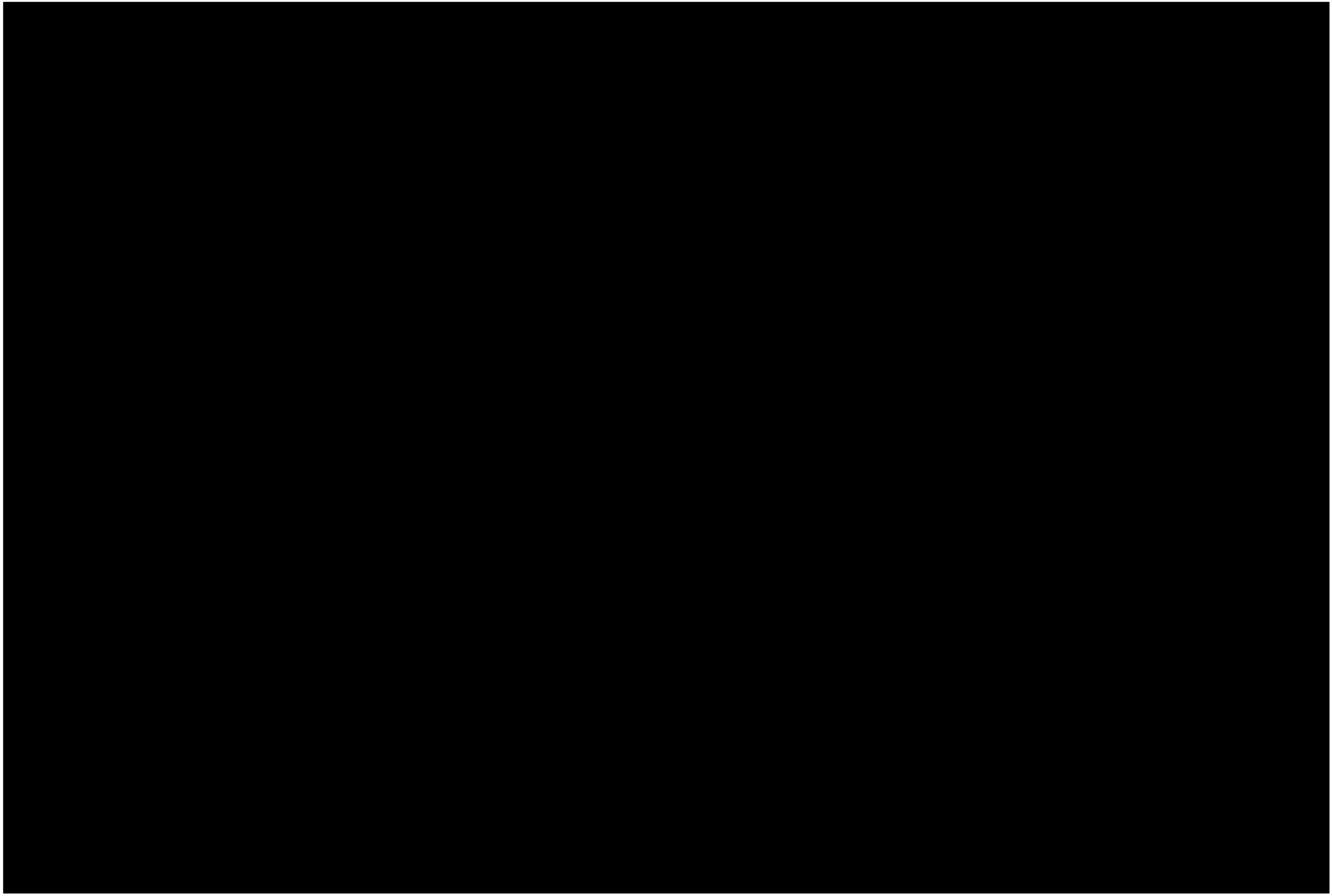
The informed consent form both in paper shall be signed and dated by the patient and the investigator or his/her designee. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the Investigator. A copy of each signed consent form must be provided to the patient. All the original signed and dated consent forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

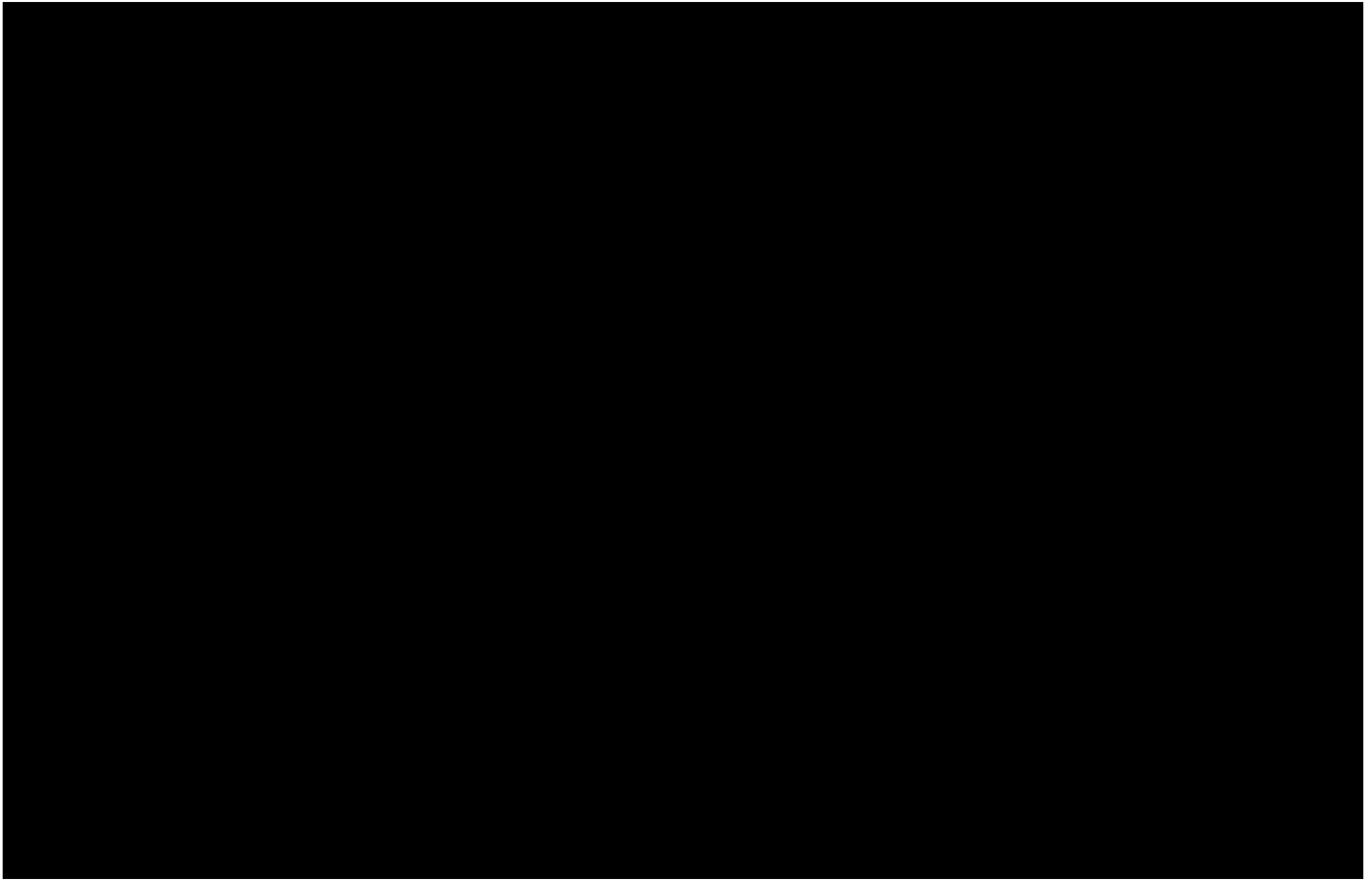
The ICF signature by both parts (including ICF version) should be documented in the patient medical record.

After informed consent has been obtained, the patient will be allocated a patient identifier and evaluated to determine study eligibility.

6.1 SCHEDULE OF VISITS

The schedule of visits, including the timing of examinations and assessments is presented in Table 4.





The following procedures and examinations **must respect the delegation of functions log**:

- done according to local law/regulations
- defined to maintain the masking
- documented and filed in the ISF.

6.1.1 Screening period

Visit #1: Screening visit

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

- Time of the measurements will be recorded
- Information of the patient and signature of the informed consent must be obtained by the patient and the investigator prior to initiation of any study-specific procedures (can be done before this visit)
- Demography
- History of the glaucoma or OHT
- Questioning about ocular medical and surgical history other than the studied disease
- Questioning about systemic medical and surgical history
- Questioning about previous and concomitant ocular and non-ocular treatments (including contraception, if applicable)
- Measurement of far BCVA
- Automated visual field (if not done in the 3 previous months and/or results not available). In case visual field would have to be performed at Visit# 5 or premature treatment discontinuation Visit the same type of device and the same program must be used
- Slit lamp examination for measuring:
  - Measurement of conjunctival hyperemia with [redacted] photographic scale
  - Score of each ocular sign
  - Anterior chamber examination for assessing Tyndall effect
  - Conjunctival staining with [redacted] grid (lissamine green staining)
  - Corneal staining with [redacted] grid scheme (fluorescein staining)
- Fundus examination
- **IOP Measurements performed at 8:00 AM (±30 min)**
- Corneal thickness measurement
- CEC assessments
- Gonioscopy
- Questioning about AEs
- Verification of inclusion and exclusion criteria
- Patient card dispensation
- Status of the patient.

The investigator must ensure that there is no interaction between the exams respecting sufficient time between them.

Naïve patients may be randomized the same day as screening visit under the following condition:

- IOP measurements should be done at 8:00 AM, 10:00 AM, 4:00 PM (±30 min) with AM measurements of IOP at least 1.5 (90 min) hours apart in order to check IOP eligibility criteria and the Visit#1 will be recorded as the Randomization visit (Visit #2, D1).
- IOP measurements should be done by the **same masked investigator/designee** and using the same calibrated Goldmann applanation tonometer at all other visits.

If it's not possible to randomize the patient the same day, the Randomization visit must be scheduled within a maximum of 14 days.

Patients using ocular hypotensive medication before Screening visit

Instructions will be given to the patient. The patient must be willing to discontinue their current antiglaucoma treatment for the specified washout period prior to Visit #2 (D1), in order to determine their IOP eligibility.

The next visit must be scheduled no later than 8:00 AM (±30 min) between a minimum of 4 day and a maximum of 31 days (according to the previous antiglaucoma treatment) after Visit #1.

<u>During the washout period, the patient may attend the following visits:</u>

Optional Visit #1.1: Optional visit planned according to the investigator´s judgement at any time during the washout period for intraocular pressure (IOP) monitoring:

Visit #1.1 will consist of the following procedures and examinations:

- Time of the measurement will be recorded
- Questioning about AE and previous/concomitant treatments will be done
- According to IOP assessment and investigator judgement:
  - Patient will continue the washout period until Visit #1.2

    OR
  - Patient will be withdrawn from the study and the investigator will ensure the continuity of antiglaucoma medication as per routine clinical practice.

Visit #1.2

Patients will be required to visit the investigators site and have their IOP measurement taken at 8:00 AM after the washout period defined by the previous treatment (from 5 days to 28 days).

Visit #2 will consist of the following procedures and examinations to be done according to the following order and in each eye by **<u>respecting the delegation of functions defined to maintain the masking</u>**

- Time of the measurement will be recorded
- Questioning about AE and previous/concomitant treatments will be done
- **IOP Measurements performed at 8:00 AM (±30 min) IOP have to be performed by the masked investigator**
  - If the investigator considers the washout period as sufficient (the baseline IOP meets the entry requirement), the visit will be recorded as the **Randomization visit** (Visit #2, D1)

OR

- If the investigator considers the washout period as incomplete (the baseline IOP does not meet the entry requirement) and decide to extend the washout period of the patient (up to a maximum of 7 days), the visit will be recorded as the **Visit #1.2**.

If the patient is withdrawn from the study, the investigator will ensure the continuity of antiglaucoma medication as per routine clinical practice.

6.1.2 Treatment Period

Examinations and questionnaires marked with a (*) MUST be performed by the SAME masked investigator for who performed the assessment at the Randomization visit

Visit #2: *Randomization* visit (D1)

Visit #2 will consist of the following procedures and examinations to be done according to the following order and in each eye by **respecting the delegation of functions defined to maintain the masking**

- Time of the measurements will be recorded.
- **Questioning about previous and concomitant ocular and non-ocular treatments***
- **Questioning about ocular symptoms***
- **Measurement of far BCVA***
- **Slit lamp examination** will be done, by the **same masked investigator/designee** for all following visits, for measuring in each eye*:
  - **Measurement of conjunctival hyperemia with [redacted] photographic scale**
  - **Score of each ocular sign**
  - **Anterior chamber examination for assessing Tyndall effect**
  - **Conjunctival staining with [redacted] grid (lissamine green staining)**
  - **Corneal staining with [redacted] grid scheme (fluorescein staining)**
- **IOP Measurements*** at 8:00 AM, 10:00 AM and 4:00 PM (each ±30 min) with AM measurements of IOP at least 1.5 (90 min) hours apart. For each timepoint, measurements of IOP have to be performed by the **same masked investigator** using the same calibrated Goldmann applanation tonometer. A staff member will read and transcribe the IOP values (readout of the tonometer).
- CEC assessments with images:
  - Central photographs will be performed in each eye
  - Anonymized photos will be collected for central reading
- **Questioning about AE***
- Urine pregnancy test (if applicable) (to be done at any time during the visit)
- Verification of inclusion and exclusion criteria
- Status of the patient: inclusion or screen failure indicating the main criteria not met
- **Randomization (IRT) and IMP prescription according to allocated IMP number*.**

By the unmasked team member:

- IMP dispensation according to allocated IMP number for 2 weeks given explanations to the patient on how and when to use the IMP
- Patient daily diary dispensation and given explanations to the patient on how to complete the diary
- Given instructions to bring back all IMP (used and not used) in their original package and the completed daily diary at the next visit to an unmasked team and not the masked investigator.
- Given instruction not to share any information on the IMP with the **masked investigator**

The next visit must be scheduled on the appropriate day (Day 15±2 days) with IOP measurement at 8:00 AM (±30 min).

Visit #3 –W2 - Day 15 (±2 days)

Visit #3 will consist of the following procedures and examinations to be done according to the following order and in each eye by respecting the delegation of functions defined to maintain the masking.

By the unmasked team member:

The **unmasked team member** counts the number of IMP remaining in the returned pack, completes and validates the accountability log (used, not used, not returned IMP). In addition to returned IMP, he/she questions the patient on the IMP compliance (number of missing doses, if any, modification of instillation time) compares with the information reported by the patient in the daily diary and records the details in the unmasked file. Information of compliance will be shared with masked investigator/designee employing a masked approach.

By the masked investigator/designee for selected tasks (the same as at the Randomization visit):

- Time of the measurements will be recorded.
- **Questioning about concomitant ocular and non-ocular treatments***
- **Questioning about ocular symptoms immediately after drop instillation***
- **Questioning about ocular symptoms throughout the day***
- **Measurement of far BCVA***
- **Slit lamp examination** will be done, by the same masked investigator as Randomization visit for measuring in each eye *:
  - **Measurement of conjunctival hyperemia with [redacted] photographic scale**
  - **Score of each ocular sign**
  - **Anterior chamber examination for assessing Tyndall effect**
  - **Conjunctival staining with [redacted] grid (lissamine green staining)**
  - **Corneal staining with [redacted] grid scheme (fluorescein staining)**
- Fundus examination in both eyes if the investigator judges that it is necessary
- **IOP Measurements*** at 8:00 AM, 10:00 AM and 4:00 PM (each ±30 min) with AM measurements of IOP at least 1.5 (90 min) hours apart. For each timepoint, measurements of IOP have to be performed by **the same masked investigator** using the same calibrated Goldmann applanation tonometer as Randomization visit. A staff member will read and transcribe the IOP values (readout of the tonometer).
- **Questioning about AE***
- **Assessment of the efficacy and the ocular tolerance by the investigator***

- **Assessment of the ocular tolerance by the patient***
- Status of the patient
- IMP prescription according to allocated IMP number (IRT).

The next visit must be scheduled on the appropriate day (Day 29±3 days) with IOP measurement at 8:00 AM (±30 min).

By the unmasked team member:

- IMP dispensation according to allocated IMP number for 2 weeks given explanations to the patient on how and when to use the IMP
- Patient daily diary dispensation and given explanations to the patient on how to complete the diary
- Given instructions to bring back all IMP (used and not used) in their original package and the completed daily diary at the next visit to an unmasked team and not the masked investigator.

Given instruction not to share any information on the IMP with the **masked investigator.**

Visit #4 – W4 - Day 29 (±3 days)

Visit #4 will consist of the following procedures and examinations to be done according to the following order and in each eye by respecting the delegation of functions defined to maintain the masking.

By the unmasked team member:

The **unmasked team member** counts the number of IMP remaining in the returned pack, completes and validates the accountability log (used, not used, not returned IMP). In addition to returned IMP, he/she questions the patient on the IMP compliance (number of missing doses, if any, modification of instillation time) compares with the information reported by the patient in the daily diary and records the details in the unmasked file. Information of compliance will be shared with **masked investigator/designee** employing a masked approach.

By the masked investigator/designee for selected tasks (the same as at the Randomization visit):

- Time of the measurements will be recorded
- **Questioning about concomitant ocular and non-ocular treatments***
- **Questioning about ocular symptoms immediately after drop instillation***
- **Questioning about ocular symptoms throughout the day***
- **Measurement of far BCVA***
- **Slit lamp examination** will be done, by the same masked investigator as Randomization visit for measuring in each eye*:
  - **Measurement of conjunctival hyperemia with [redacted] photographic scale**
  - **Score of each ocular sign**
  - **Anterior chamber examination for assessing Tyndall effect**
  - **Conjunctival staining with [redacted] grid (lissamine green staining)**
  - **Corneal staining with [redacted] grid scheme (fluorescein staining)**
- Fundus examination in both eyes if the investigator judges that it is necessary
- **IOP Measurements*** at 8:00 AM, 10:00 AM and 4:00 PM (each ±30 min) with AM measurements of IOP at least 1.5 (90 min) hours apart. For each timepoint, measurements of IOP have to be performed by the same masked investigator using the same calibrated Goldmann applanation tonometer as

Randomization visit. A staff member will read and transcribe the IOP values (readout of the tonometer)

- **Questioning about AE***
- **Assessment of the efficacy and the ocular tolerance by the investigator***
- **Assessment of the ocular tolerance by the patient***
- Status of the patient.
- IMP prescription according to allocated IMP number (IRT).

By the unmasked team member:

- IMP dispensation according to allocated IMP number for 2 weeks given explanations to the patient on how and when to use the IMP
- Patient daily diary dispensation and given explanations to the patient on how to complete the diary
- Given instructions to bring back all IMP (used and not used) in their original package and the completed daily diary at the next visit to an unmasked team and not the masked investigator.

Given instruction not to share any information on the IMP with the **masked investigator**

The next visit must be scheduled on the appropriate day (Day 50±3 days) with IOP measurement at 8:00 AM (±30 min).

Visit #5 – W7 - End of treatment visit, Day 50 (±3 Days)

Visit #5 will consist of the following procedures and examinations to be done according to the following order and in each eye by respecting the delegation of functions defined to maintain the masking.

By the unmasked team member:

The unmasked team member counts the number of IMP remaining in the returned pack, completes and validates the accountability log (used, not used, not returned IMP). In addition to returned IMP, he/she questions the patient on the IMP compliance (number of missing doses, if any, modification of instillation time) compares with the information reported by the patient in the daily diary and records the details in the unmasked file. Information of compliance will be shared with masked investigator/designee employing a masked approach.

By the masked investigator or delegate for selected tasks (the same as at the Randomization visit):

- Time of the measurement will be recorded
- **Questioning about concomitant ocular and non-ocular treatments***
- Q**uestioning about ocular symptoms immediately after drop instillation***
- **Questioning about ocular symptoms throughout the day***
- **Measurement of far BCVA***
- Automated visual filed in both eyes if the investigator judges that it is necessary. If this is the case, the assessment must be done with the same type of device and the same program as Visit #1
- **Slit lamp examination** will be done, by the same masked investigator as Randomization visit for measuring in each eye *:
  - **Measurement of conjunctival hyperemia with [redacted] photographic scale**
  - **Score of each ocular sign**

- **Anterior chamber examination for assessing Tyndall effect**
- **Conjunctival staining with [redacted] grid (lissamine green staining)**
- **Corneal staining with [redacted] grid scheme (fluorescein staining)**

- Fundus examination
- **IOP Measurements*** at 8:00 AM, 10:00 AM and 4:00 PM (each ±30 min) with AM measurements of IOP at least 1.5 (90 min) hours apart. For each timepoint, measurements of IOP have to be performed **by the same masked investigator** using the same calibrated Goldmann applanation tonometer as Randomization visit. A staff member will read and transcribe the IOP values (readout of the tonometer)
- Corneal thickness measurement
- CEC assessments with images:
  - Central photographs will be performed in each eye
  - Anonymized photos will be collected for central reading
- **Questioning about AE***
- **Assessment of the efficacy and the ocular tolerance by the investigator***
- **Assessment of the ocular tolerance by the patient***
- Urine pregnancy test (if applicable) (to be done at any time during the visit)
- Status of the patient
- The investigator will ensure the continuity of antiglaucoma medication as per routine clinical practice.

At the end of the IMP masking period, the masked investigator/ designee should confirm that she/he has not been unmasked during the study.

6.1.3 Premature treatment discontinuation visit

A patient who prematurely discontinues the study treatment should have, if possible, a premature study treatment discontinuation visit. This visit should take place as soon as possible after the patient stops taking IMP.

The investigator will ensure the continuity of antiglaucoma medication as per routine clinical practice.

Then the patient must perform all visits and study procedures planned until visit #5 (W7). In this case, the maximum number of visits could be 8.

6.1.4 Unscheduled visit

If needed (for example: safety reasons, patient's request), the same masked investigator as at randomization may ask the patient to visit the site for ophthalmic and/or systemic assessments. This visit should be organized directly by the masked investigator site as soon as he judges necessary. According to the masked investigator's judgement, the required examinations as scheduled at the premature study treatment discontinuation will be performed.

6.1.5 Adaptive follow-up of patients prematurely withdrawn due to an exceptional circumstance (e.g., COVID-19 pandemic)

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

Either the patient may continue the study when he/she can follow the protocol requirements safely and in accordance with the national/regional recommendations or the patient may discontinue the IMP.

If the patient discontinued due to exceptional circumstance (inability to perform onsite visits), he/she will perform a **remote** premature discontinuation visit (phone call) as soon as possible.

The reason of study discontinuations must be clearly stated in the e-CRF and patient's file.

During the remote premature discontinuation visit, the main requirements will be as follows:

- Check the IMP compliance with the patient (**unmasked team member)**
- Instruct the patient to stop the IMP and keep used and unused IMPs for later return
- Ensure the continuity of anti-glaucoma medication as per routine clinical practice
- Collect AE/SAE and any changes in concomitant treatments
- Record the phone call and all information collected in the patient medical record and e-CRF.

An unscheduled visit will be planned as soon as possible. All procedures and examinations will be performed as scheduled for the premature study treatment discontinuation visit, as described in Section 6.1.5.

The patient is asked to return the used and unused IMPs and the daily diary to the **unmasked team.**

Record the visit and all information collected in the patient medical record and e-CRF.

6.2 STUDY PROCEDURES

Timing of procedures is presented in Table 2.

6.2.1 Demographics and Screening Characteristics

The following characteristics will be collected:

- Year of birth
- Sex (Male, Female)
- For female, childbearing potential (Yes/No) and birth control method
- Race (Indigenous and Native American, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Iris color (Blue, Gray, Green, Brown, Hazel, Other)
- Medical and surgical history:
  - Ocular medical and surgical history with relevant diagnosis other than the studied disease
  - Systemic medical and surgical history with relevant diagnosis
- History of glaucoma or OHT:
  - Diagnosis for each eye (OHT/OAG)
  - Date of onset of the diagnosis in each eye (months/year)
  - Type of previous antiglaucoma treatment *(if applicable)*
  - Surgical history related to the glaucoma or OHT in each eye
- Previous (within 3 months before the screening visit) concomitant ocular and non-ocular medications.

6.2.2 Efficacy measures

6.2.2.1 IOP measurement in each eye

At screening visit, IOP should be measured at 8:00 AM (±30 min).

At visits D1, W2, W4, W7 or premature study treatment discontinuation visit, IOP should be measured at three timepoints 8:00 AM, 10:00 AM (at least 1.5 hours apart) and 4:00 PM (each ±30 min).

At optional Visit #1.1, IOP may be performed at any times.

IOP measurements should be done in each eye by the **same masked investigator/designee** and using the **same calibrated Goldmann applanation tonometer for all visits from Randomization visit onwards.**

One drop of anesthetic and one drop of fluorescein will be administered in each eye before IOP measurement.

Two measurements have to be taken in each eye at each timepoint. If the 2 readings differ by more than 2 mmHg, then a third reading is to be taken.

Once the **masked investigator/designee** (The same for all visits from Randomization visit) reaches the correct applanation effect in the slit lamp, a second staff member will read and transcribe the IOP values (readout of the tonometer) in the patient medical record.

The tonometer will be appropriately calibrated, the monthly check of the calibration with weight has to be documented and the same instrument will be used for the entire study.

6.2.2.2 Efficacy assessment by the investigator

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

"Do you consider the IMP efficacy as:

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

6.2.3 Safety measures

6.2.3.1 Adverse events

Ocular and systemic AEs will be collected at each visits and by the same masked investigator from randomization 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.

6.2.3.2 Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

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

An AE may include, but is not limited to:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the IMP
- Event unrelated to participation in the clinical study
- A combination of one or more of these factors.

Adverse Reaction (AR): All untoward and unintended responses to an IMP related to any dose administered.

Treatment-emergent AE (TEAE): is defined as an AE that occurs or that worsens in severity after at least one dose of IMP has been administered.

Serious Adverse Event (SAE) any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization, or a prolongation hospitalization
- Results in persistent or significant disability incapacity

- Associated with congenital anomaly or birth defect
- Other medically important serious events (occurs with an accidental or voluntary overdose, pregnancy, associated with the development of cancer or any other unfavorable medical event which is not fatal, life-threatening, and does not require hospitalization, but requires urgent and intensive treatment).

Serious Adverse Reaction (SAR): An adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Suspected Unexpected SAR (SUSAR): is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

New events: new events related to the conduct of a study or the development of an IMP likely to affect the safety of patients, such as:

- a SAE which could be associated with the study procedures and which could modify the conduct of the study
- a significant hazard to the patient population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt of a study for safety reasons if the study is conducted with the same IMPs in another country by the same Sponsor.

Adverse Event of Special Interest (AESI): (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate.

6.2.3.3 Assessment of AE

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

6.2.3.4 Severity

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 hospitalization) 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.

6.2.3.5 Causality Relatedness to the IMP

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

Related: The AE is related to the tested product and cannot be reasonably explained by other factors (e.g., concomitant therapy, patient condition, and/or other intervention)

Not related: A simultaneous disease, a simultaneous treatment or any other known condition clearly triggers the AE.

6.2.3.5.1 *Recording AE*

Adverse event reporting will extend from signing of informed consent until the final study visit. If the investigator is aware of an adverse event occurring within one month after final study visit (Week 7) and that he considers there is a causal relationship with the IMP, the AE should be reported in the e-CRF.

All AEs, regardless of the relationship to IP, will be recorded in the e-CRF.

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

6.2.3.5.2 *Reporting of adverse events of special interest*

Based on observation in previous studies with ROCKi, the following AEs will be considered as AESI, if judged significant by the investigator:

- All AEs related to CEC
- All AEs related to visual impairment (partial or total visual acuity loss)
- Corneal opacity
- Lens opacity/cataract
- Corneal verticillate

These AEs will be recorded and reported as described in the Section 6.2.3.5.1

6.2.3.5.3 *Reporting SAE*

Reporting by the investigator to the Sponsor

In case of SAE and follow-up, the investigator must:

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

Once signed (by an electronic signature), the SAE form will generate an alert automatically sent by email to

[redacted]

In case of e-CRF breakdown, a paper copy of the SAE form will be available in the ISF and will have to be manually completed, dated and signed by the investigator and sent by email to: [redacted] or fax it to:

[redacted]

In that case, the original signature page must be sent within 24 hours, to the following address by mail:

GlobalSafety and MedInfo specialist Department

Laboratoires THÉA

[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 IMP. The sponsor must promptly investigate all safety information it receives. Additional follow-up reports must be sent back to Laboratoires THÉA within 24 hours upon receipt of follow-up information query.

Any follow-up will be transmitted within 8 additional calendar days.

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
- Study medication administration record

The Global Safety Department will have read access to this information in the e-CRF.

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 IMP, and therefore deemed as a possible SAR, the investigator must report the SAE to the Sponsor immediately.

As for all other study documents, the investigator will retain a copy of the SAE form for 25 years.

Reporting by the Sponsor/CRO to Competent authorities/ Ethics Committees/ Institutional Review Board

All suspected adverse reaction related to an investigational product which occur in the concerned study, and that are both unexpected and serious (SUSARs) must be reported to the Competent Authorities and Independent Ethics Committees/ Institutional Review Board by Laboratoires THÉA and/or the CRO as described in the safety management plan.

- as soon as possible but not later than 7 calendar days in case of fatal or life threatening SUSARs
- as soon as possible but not later than 15 calendar days for all other SUSARs and for all follow-up IND safety reports.

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

6.2.3.5.4 *Follow-up of patient due to an AE/SAE*

During the study

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

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 stabilized at a level acceptable to the investigator and/or 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 stabilized at a level acceptable to the investigator and Medical expert and/or until completion of the “Last Patient Last Visit”.

After the patient terminated the study

The investigator is responsible for ensuring the follow-up of any patient who experiences:

- an AE related to IMP

- An AESI
- SAE
- An any AE at the investigator's discretion or sponsor's discretion.

until the event has resolved or, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator and medical expert or until there is a satisfactory explanation for the changes observed.

6.2.3.5.5 *Management of pregnancy*

In case of the investigator or an appropriate qualified physician is informed that a patient becomes pregnant while taking IMPs, she will be immediately withdrawn from the study and she will be followed until the outcome of the birth is available. Handling of a pregnancy occurring throughout the study follows the same reporting procedure as per an SAE notification.

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.

Upon medically confirmed pregnancy during the study the investigator must:

- Report immediately (maximum 24 hours) the pregnancy status to the Sponsor using the email [redacted]
- Discontinue the IMP for the participant and withdraw the participant from the study
- Perform / ensure assessment until delivery of a thorough study of the fetus
- Remain responsible for any medical advice he/she might seek thus making appropriate decision upon pregnancy,
- Report to the Sponsor follow-up data/update(s) using the SAE form.

This procedure also applies if the female partner of the study patient become pregnant during the study. Then the male patient enrolled in this study should inform the Investigator upon a medically confirmed pregnancy of his partner. If the partner or the caregiver of the newborn consents, data from pregnancy status will be collected and reported thereafter by the investigator. Prior to any data collection, a specific duly designed ICF will be completed.

6.2.3.6 Automated visual field: Standard automated perimetry

Visual field testing in each eye will be performed using the same type of device with the same glaucoma program (24-2 SITA Standard) and evaluation of the visual field defect indices (periodic maintenance is observed according to manufacturer instructions).

At the Visit #1, it will be specified if there is

- an absolute defect in the 10-degree central point
- a severe visual field loss
- a risk of visual field worsening as a consequence of participation in the study.

If AVF is required at Visit #5 or at premature study treatment Discontinuation visit, the investigator will have to indicate if the visual field is stable. If the visual field is not stable, the investigator will have to specify if it is clinically significant or not and will report an AE accordingly.

6.2.3.7 Visual acuity

BCVA will be measured in each eye using the same chart (for example a Snellen chart) throughout the study. It can be expressed using units as, LogMAR or Snellen notation. It will be analyzed after conversion in LogMAR (see Appendix 11.1).

6.2.3.8 Gonioscopy: measure of iridocorneal angle

The iridocorneal angle (situated on the circumference of the anterior chamber between the sides of the cornea and sclera and the base of the iris and the anterior surface of the ciliary body) structure will be analyzed with a gonioscope.

At the Visit#1, the IAC will be assessed using grading Schaffer system in 0-5 grades which 4 is wide open and 0 is closed:

Grade 0:	(0°) Closed angle: iridocorneal contact is present (unable to identify the apex of the corneal wedge)
Slit angle:	No obvious iridocorneal contact but no angle structure can be identified; greatest danger of imminent closure
Grade 1:	(10°) Very narrow angle: Schwalbe's line can be identified; angle closure is not inevitable but risk is high
Grade 2:	(20°) Moderately narrow angle: Trabeculum can be identified; angle closure is possible but unlikely
Grade 3:	(25° to 35°) Open angle: Scleral spur can be identified; incapable of closure
Grade 4:	(35-45°) Widest angle: Ciliary body can be visualized with ease; incapable of closure

6.2.3.9 Slit Lamp Examination

The following criteria will be assessed with the corresponding scores:

- Conjunctival hyperemia

The level of severity of conjunctival hyperemia will be scored using the [redacted] photographic scale (0 to 4) in each eye (see Appendix 11.3).

- Ocular signs

The following ocular signs will be evaluated in each eye using the slit lamp examination.

- Eyelid examination: eyelid oedema, eyelid erythema, blepharitis
- Conjunctival examination: folliculo-papillary conjunctivitis (after eversion of the superior and inferior eyelids), conjunctival oedema, conjunctival hemorrhage
- Corneal examination: corneal neovascularization, corneal opacity, corneal oedema, cornea verticillata.
- Eyelashes changes
- Iris hyperpigmentation.

in 0-3 scale:

(0) = None

(1) = Mild

(2) = Moderate

(3) = Severe

- Anterior chamber examination/or Tyndall effect

The following criteria will be assessed in each eye:

Tyndall effect

Cells in field will be scored using the [redacted] Grading Scheme (using 1mm slit beam):

- 0 = < 1 cell
- 0.5+ = 1 to 5 cells
- 1+ = 6 to 15 cells
- 2+ = 16 to 25 cells
- 3+ = 26 to 50 cells
- 4+ = 50+ cells.

Flare will be scored using the [redacted] Grading Scheme (using 1mm slit beam):

- 0 = None
- 1+ = Faint
- 2+ = Moderate (iris/lens details clear)
- 3+ = Marked (iris/lens details hazy)
- 4+ = Intense (fibrin/plastic aqueous).

- Conjunctival lissamine green staining

Nasal and temporal conjunctival staining will be graded in each of the six conjunctival zones following lissamine green instillation using [redacted] scale in each eye [redacted]

The score of each zone will be recorded in the e-CRF and in the participant medical record. The total score will be calculated automatically in the e-CRF.

- Corneal fluorescein staining

Approximately 2.5-3.0 minutes following fluorescein instillation, corneal staining will be evaluated in each eye. Fluorescein with and without preservative are authorized. However, the use of preservative-free products is recommended, and the same type of product will be used for the same patient throughout the study. Corneal staining will be scored as following in each of the five corneal zones using the [redacted] scale (A: Central, B: Superior, C: Temporal, D: Nasal, E: Inferior) ([redacted]

0 = Normal, negative slit lamp findings.

1 = Mild, superficial stippling.

2 = Moderate, punctuate staining including superficial abrasion of the cornea.

3 = Severe, abrasion or corneal erosion, deep corneal or recurrent erosion.

The score of each zone will be recorded in the e-CRF and in the participant medical record. The total score (0-15) will be calculated automatically in the e-CRF.

6.2.3.10 Fundus examination

Fundus examination without pupil dilation in each eye.

At the Visit#1: The cup to disk ratio (C/D) will be measured both horizontally and vertically, with the highest value recorded for each eye.

Any abnormality in the posterior segment will also be recorded.

At Visit#5 or premature study treatment discontinuation visit (or at Visit #3 and Visit# 4 if the investigator judges fundus examination will be assessed is necessary) the investigator will indicate if any abnormalities have been detected in the posterior segment. If yes, abnormalities will be specified for each eye.

6.2.3.11 Central corneal thickness measurement

Measurement of the central corneal thickness will be performed with a calibrated ultrasound pachymeter (periodic maintenance is observed according to manufacturer instructions).

The central corneal thickness (in µm) will be measured in each eye.

6.2.3.12 CEC assessments

CEC assessments at Visit #1 by site

The CEC density (in cell/mm²) will be assessed in each eye at Visit #1 with a calibrated specular microscopy (periodic maintenance is observed and documented).

CEC assessments reviewed by central reading (Visit #2 and Visit #5 or premature treatment discontinuation visit)

The central CEC assessments will be assessed in each eye with the same calibrated specular microscopy (periodic maintenance is observed and documented).

The following parameters will be measured:

- Central CEC density (in cell/mm²)
- Hexagonal cells ratio (in %)
- Coefficient of variation.

Any detected abnormality will be recorded.

Central photographs will be performed in each eye and anonymized photos will be collected. These anonymized photos will be reviewed for assessment by an independent reading center. A dedicated secure transfer supporting CEC assessment data reviewing, analysis and storage might be used: the anonymized photos, values, date and hour of the exam with name of the examiner.

All instructions concerning photos (method, anonymization, storage and reading) will be detailed in a specific study manual.

6.2.3.13 Ocular tolerance assessment by the Investigator

The masked investigator has to answer to the following question:

"Do you consider the ocular tolerance of the study treatment as?

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

6.2.3.14 Ocular tolerance assessment by the patient

The masked investigator has to ask the participant the following question:

"Do you consider the ocular tolerance of the study treatment as?

- Very satisfactory
- Satisfactory
- Not very satisfactory

- Unsatisfactory".

The ocular tolerance will be assessed by the participant.

6.2.3.15 Ocular symptoms immediately after drop instillation

The severity of ocular symptoms **immediately after drop instillation**: will be assessed by the masked Investigator (or masked delegates) asking the patient:

"Have you felt any ocular discomfort/unusual sensation IMMEDIATELY AFTER DROP INSTILLATION since the last visit?"

The following symptoms will be evaluated immediately after IMP instillation:

- Burning/irritation
- Stinging/Eye pain
- Itching/Pruritus
- Ocular redness
- Tearing
- Eye dryness feeling
- Foreign body sensation
- Blurred vision.

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

0 = Absent,

1 = Mild, present but not disturbing

2 = Moderate, disturbing

3 = Severe, very distressing.

For each symptom, the usual duration and the frequency will be recorded. Frequency will be assessed as follows:

- Very often: ≥ 80% of instillation/administration
- Often: ≥ 40% et < 80% of instillation/administration
- Not very often: ≥ 10% et < 40% of instillation/administration
- Rarely: < 10% of instillation/administration.

These procedures will be assessed globally for both eyes

6.2.3.16 Ocular symptoms throughout the day

The severity of ocular symptoms occurring throughout the day (excluding ocular symptoms immediately after drop instillation) will be assessed by the masked Investigator (or masked delegates) asking the patient:

Visit ≠2: "How do you judge the severity of the following ocular symptoms throughout the day?"

Visit ≠3, ≠4 and ≠5 or premature study treatment discontinuation: "How do you judge the severity of the following ocular symptoms (excluding ocular symptoms immediately after drop instillation) throughout the day?"

The following symptoms will be evaluated:

- Burning/irritation

- Stinging/Eye pain
- Itching/Pruritus
- Ocular redness
- Tearing
- Eye dryness feeling
- Foreign body sensation.

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

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.

These procedures will be assessed globally for both eyes.

6.2.3.17 Treatment compliance evaluation

Participant will receive a participant diary after the randomization. Each day from the first to the last IMP instillation participant will record in his/her participant diary:

- Date, time of IMP instillation and eyes instilled.

The patient will return all IMPs whether used or unused at each visit. The number of returned / unreturned IMPs will be recorded in the accountability log by the **unmasked team member.**

The **unmasked team member** will assess compliance by questioning the patient, checking the patient daily diary during the visit (e.g., if there was any treatment interruption or missed instillation) and by the number of used and unused IMPs.

The following information will be reported for each period in the e-CRF:

- Date and time of last IMP instillation
- Missed and daily dose modifications

6.2.4 IMP Complaints

A complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product after it is released for distribution. A complaint is any expression of dissatisfaction with a product or service marketed.

If the investigator/patient observes any abnormality and/or complaint of T4090 the investigator must report to [redacted] **within 24 hours of being aware of it (**Appendix 11.7**)**.

Laboratoires THÉA must

- review all complaint 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.
- (if applicable) report to regulatory authorities, IRB, investigators, within the required time period any complaints 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 complaint with any components of the IMP and in function of the type of complaint, the Laboratoires THÉA will take the appropriate decision to maintain the security/safety of patient.

7 STATISTICAL METHODS

The statistical analysis plan (SAP) will be produced before database lock 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 clinical study report (CSR).

7.1 GENERAL CONSIDERATIONS

Continuous variables will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation, median, Q1, Q3, minimum and maximum).

Frequency distribution (counts and percentages) will be summarized for the categorical variables.

When applicable, 95% Confidence Interval (CI) of the mean will be provided for continuous variables and 95% CI of the proportion will be displayed for each modality of categorical variables.

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

Change from baseline could also be presented when necessary.

Variables recorded for each eye will be described separately for the study eye and for the contralateral eye (if applicable).

[redacted]

If not otherwise specified, baseline is defined as the last value before the first instillation for each endpoint.

The mean diurnal IOP at Day 1 will be the baseline for analysis of the mean diurnal IOP. For IOP, the value recorded at 8:00 AM at Day 1, respectively at 10:00 AM and at 4:00 PM, will be the baseline for analysis of IOP at 8:00 AM, respectively at 10:00 AM and at 4:00 PM.

[redacted]

Comparison between groups will be performed at a two-sided significance level of 5% and no adjustment of the type I error rate will be made.

7.2 ANALYSIS SETS

The following analysis sets will be considered:

- **Safety set:**

All enrolled patients, having received at least one dose of IMP and considered as-treated.

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

All randomized patients.

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

All randomized patients having received at least one dose of IMP.

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

All FAS patients without any major protocol violation (likely to seriously affect the primary outcome of the study).

[redacted]

Safety set will be the primary population for safety analysis.

FAS set will be the primary population for efficacy analysis.

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

7.3 ESTIMANDS

The primary objective of the clinical study translates directly into the clinical question of interest by defining suitable estimands. Thus, the estimand is a precise description of the treatment effect reflecting the clinical question of interest posed by the primary clinical study objective. For this study, the primary clinical question of interest is to compare the ocular hypotensive efficacy of two concentrations of T4090 ophthalmic solution with Rhopressa ophthalmic solution in terms of lowering the mean diurnal IOP at Week 7 in the study eye (*i.e.,* eye with the highest mean diurnal IOP at baseline)?".

7.3.1 Estimand for the primary objective

7.3.1.1 Treatment condition of interest

The primary treatment condition of interest is T4090, PF Kinezodianone *R* HCl 0.2% and 0.3% ophthalmic solution administered in each eye, once daily compared to preserved netarsudil 0.02% Rhopressa administered in each eye, once daily and to compare T4090, PF Kinezodianone R HCl 0.2% to T4090, PF Kinezodianone R HCl 0.3%.

7.3.1.2 Population of patients targeted by the clinical question of interest

The population targeted by the clinical question is in patients in whom both eyes were diagnosed with OHT or OAG, and further defined through the inclusion and exclusion criteria in Section 4.2 and 4.3.

7.3.1.3 Variable obtained from each patient required to address the clinical question of interest

For each patient in the study, the variable that is measured to address the clinical question is the change from baseline in the mean diurnal IOP at W7.

7.3.1.4 Handling of intercurrent events to reflect the clinical question of interest

Intercurrent events are events occurring after treatment initiation that may affect either the interpretation or the existence of the measurements associated with the clinical question of interest. [redacted]

[redacted]

7.3.1.5 Population-level summary for comparison between treatment conditions

The treatment effect will be quantified by the comparison of treatments estimated using least squares (LS) means of change from baseline in mean diurnal IOP at W7 obtained using the primary analysis Mixed Model of Repeated Measures (MMRM). The basis for comparison will be the difference between treatment groups in these LS mean differences from baseline.

[redacted]

7.4 STATISTICAL ANALYSES

7.4.1 Efficacy Analyses

7.4.1.1 Primary efficacy endpoint

Primary statistical analysis for primary estimand

The primary efficacy endpoint is the change from baseline in mean diurnal IOP at W7 post-baseline visit in the study eye.

Main Analysis of the Primary Efficacy Estimand (1)

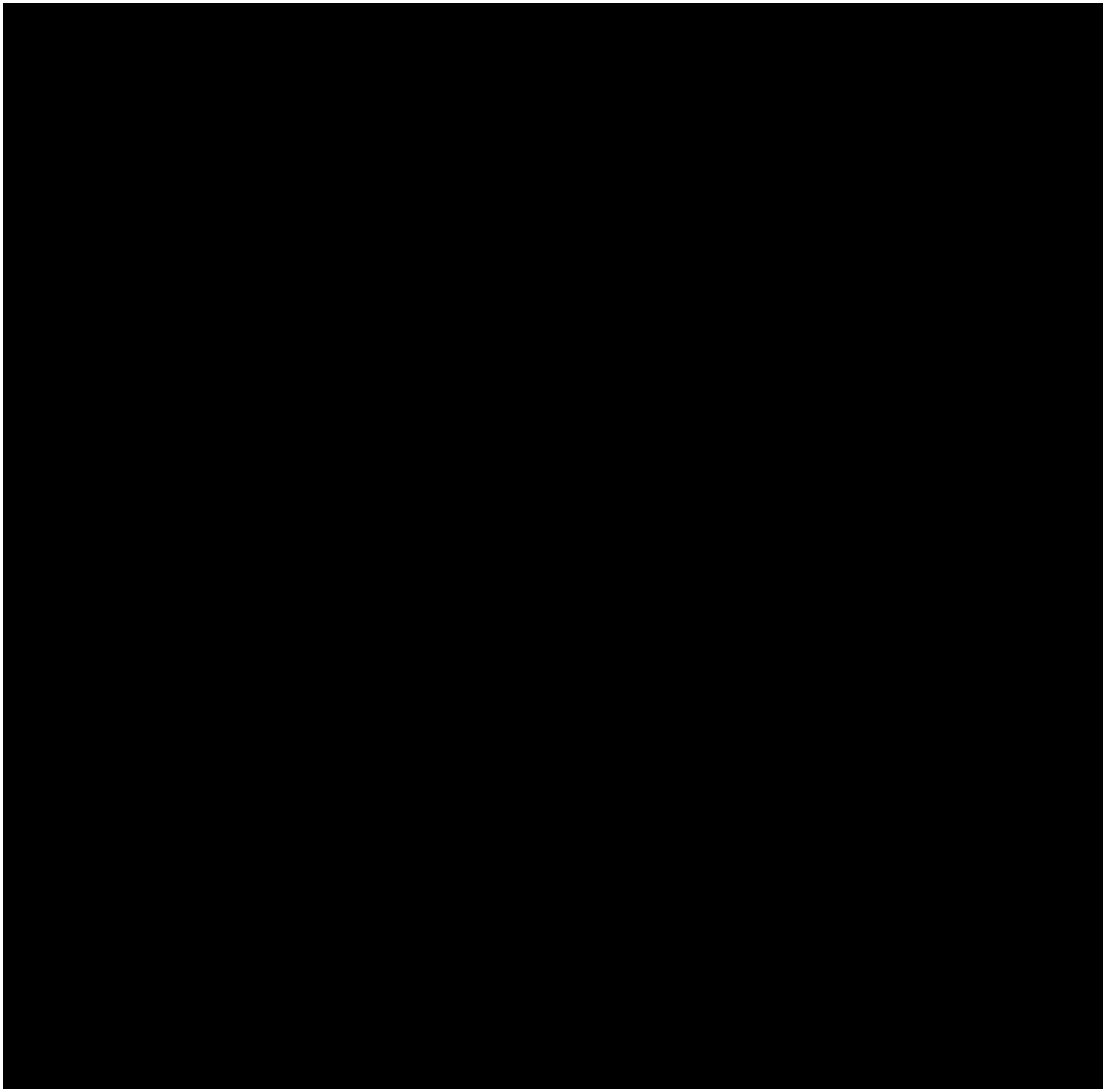
Change from Baseline (D1) at W2, W4, and W7 in mean diurnal IOP in the study eye will be evaluated using an MMRM. The model will include treatment, visit (W2, W4 and W7), baseline mean diurnal IOP, baseline IOP at 8:00 AM in class [redacted]), treatment by visit interaction, and baseline mean diurnal IOP by visit interaction as fixed factors and patient ID as a random factor. [redacted]

LS mean difference from baseline for each treatment group by visit and estimates of the difference at each visit will be provided, along with their respective 95% CIs.

Descriptive statistics for the mean and mean difference from baseline in mean diurnal IOP by visit on study eye will also be provided.

The primary efficacy endpoint will be primarily analyzed on the FAS.

[redacted]



7.4.2 Safety Analyses

Safety endpoint will be analyzed in the Safety set.

Ocular and systemic AEs

Ocular and systemic AEs reported during the study will be coded using the MedDRA dictionary.

Ocular and systemic AEs will be analyzed separately on the basis of the localization.

Summary tables will be performed on TEAEs. TEAEs are AEs that occurred after the first IMP instillation. AEs that occurred the day of the first IMP instillation will be reviewed during a blind review meeting to decide if they have to be considered as TEAE or not.

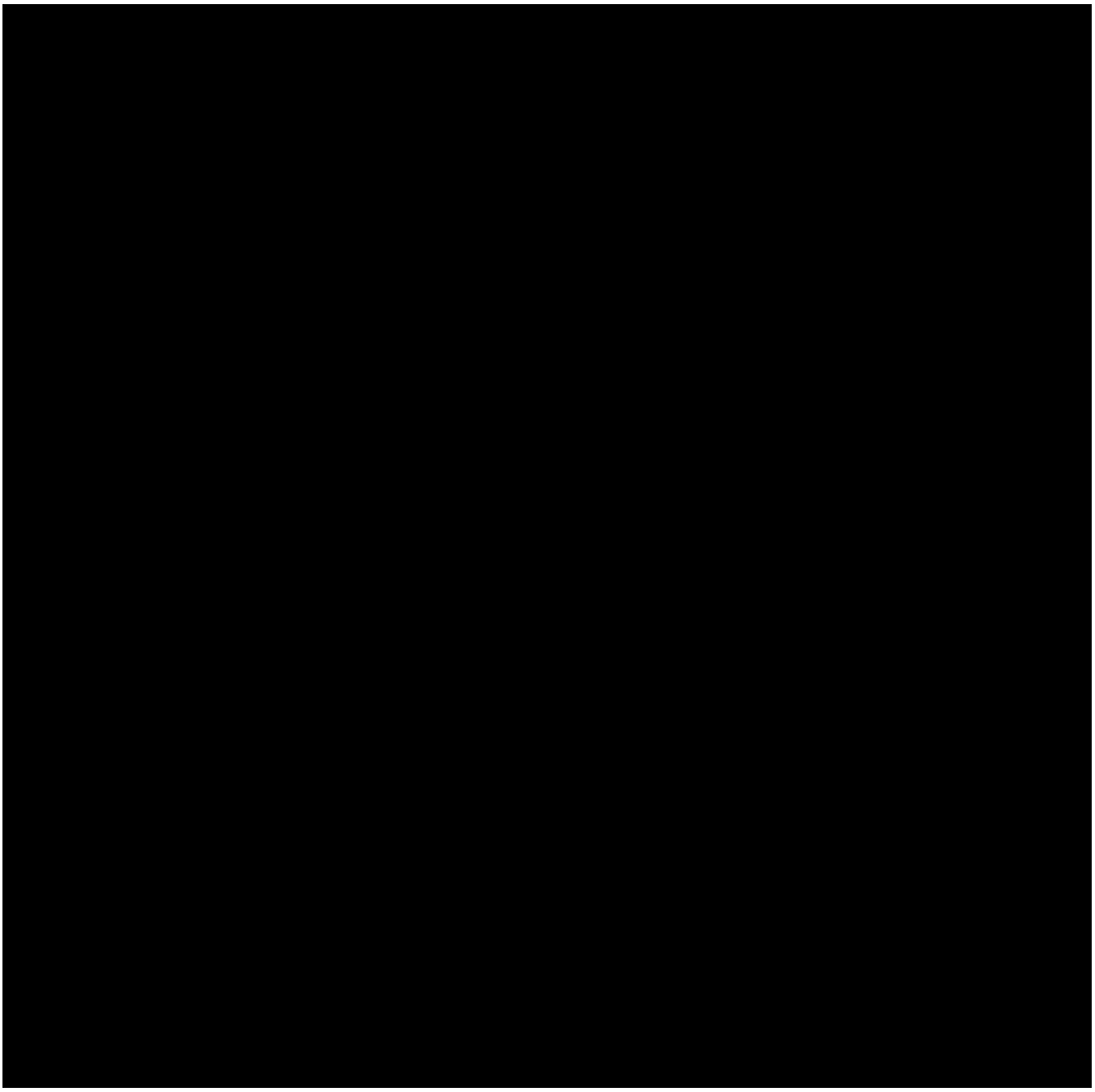
Separate descriptions of treatment-emergent ocular and systemic AEs will be performed by treatment group:

- Number and percentage of patients experiencing at least one AE, SAE, drug-related AE, and AE leading to premature study drug 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, drug-related AEs, drug-related SAEs and AEs leading to premature study drug discontinuation
- Number and percentage of patients with AEs, as well as the number of AEs, by SOC, PT, and severity
- Number and percentage of patients with AEs, as well as the number of AEs, by SOC, PT, and relationship with IMP.

Patient data listings will be provided.

[redacted]



7.5 DETERMINATION OF SAMPLE SIZE

This is a Phase II pilot study, and the analysis is to be considered as exploratory. Therefore, no formal sample size calculation will be performed.

It is planned to randomize 126 patients with a randomization scheme 1:1:1 with a stratification by baseline IOP at 8:00 AM in class).

8 ETHICAL AND LEGAL ASPECTS

8.1 GOOD CLINICAL PRACTICE

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigator comply with applicable regulatory and ICH E6 (Good Clinical Practice (GCP)) requirements as well as the ethical principles laid down in the current version of the Declaration of Helsinki and the applicable amendments, applicable FDA regulation and local regulations.

Prior to any study procedure a written informed consent must be obtained from the patient and/or his/her legal representative.

8.2 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Prior to starting the study, the CSP and other relevant documents will be submitted and approved by the IEC/IRB and/or Competent Authorities, 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 study.

Full compliance with this CSP must be sought.

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

According to the CFR21 Part. 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the study progress.

According to the CFR21 Part. 312.32, the Sponsor must notify FDA and all participating investigators the IND safety reports as described in Section 6.2.3 Upon request from FDA, the Sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

To alter the CSP, amendments must be written, approved by the appropriate personnel, and by IEC/IRB/Competent Authorities prior to 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 CSP amendment must contain specific identification of the document (e.g., the investigator's name and the CSP title and number).

The CSP 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, if applicable. Modifications must be documented in a signed amended CSP.

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

As required by the legislation, the Sponsor will promptly report the following for review or information to the IEC/IRB/Competent Authorities:

- Substantial CSP modifications
- Administrative changes
- Information on suspected unexpected SAE
- Periodic safety reports, when applicable
- Periodic reports on the progress of the study, when applicable
- New information that may affect adversely the safety of the patients or the conduct of the study.

- Serious breaches inherent to the CSP, as per regulatory requirements.

8.3 FINANCIAL INTERESTS AND ARRANGEMENTS

The Principal Investigator and investigators should provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

A clinical study agreement should be established between the Sponsor or his delegate (CRO) and the site.

8.4 DELEGATION OF INVESTIGATOR DUTIES

The Principal Investigator should ensure that all persons assisting with the study conduct are adequately informed about the clinical study protocol, any amendments to the protocol, the IMPs, and their study-related duties and functions.

The Principal Investigator should maintain a list of Investigators and other appropriately qualified and authorised persons to whom he or she has delegated significant study-related duties according to the local regulations.

8.5 DURATION OF THE STUDY

The study duration for a patient is maximum 3 months.

The study will be closed after the last patient last visit.

8.6 EARLY TERMINATION OF THE STUDY

The investigator has the right to terminate this study for any reason at any time. As far as possible, this should occur after mutual consultation with the Sponsor.

If the investigator decides to early terminate the study, he/she should promptly inform the participants, assure appropriate therapy and follow-up for the participants, and should inform the Sponsor and the regulatory authority(ies). The investigator/institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

The IRB(s) or FDA may prematurely terminate participation at the study sites for which they are responsible.

According to ICH-GCP E6 R2, if the IRB(s)/IEC(s) terminates its approval/favorable opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the Sponsor and provide it with a detailed written explanation of the termination.

Per 21 CFR 312.44, if an IND is terminated by FDA, the Sponsor shall end all clinical studies conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the IMP. A termination action may be based on deficiencies in the IND or in the conduct of a study under an IND.

The Sponsor shall have the right to terminate the study at any time and for any reason on written notice to all involved investigator sites, IRB(s) and FDA with the reasons for such withdrawal. Conditions, that may warrant early termination of the study, or an individual site include, but are not limited to, the following occurrence of:

- New events (see Section 6.2.3), for severe and/or serious AEs with the IMP in human or animal studies
- For commercial reasons

- If the Sponsor had reasons to believe that the study could not be satisfactorily completed, including, but not limited to, the reason that inadequate numbers of subjects could be enrolled, or insufficient centers found within the necessary time.

If the Sponsor terminates a study because of a safety reason, the Sponsor shall promptly inform FDA and the investigators who also should promptly inform the institution where applicable. The investigator/institution/Sponsor should promptly inform the IRB(s)/IEC(s) and provide the IRB(s)/IEC(s) a detailed written explanation of the termination.

In the case of Sponsor decides the early termination of the study due to an unreasonable and significant risk to participants, and according to 21 CFR 312.56, the Sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued.

If the study terminates prematurely, all study materials (including, IMPs, other study medication, completed, partially completed) must be returned to the Sponsor or the Sponsor's representative as if the study had been completed.

The Sponsor should ensure that study early termination and follow-up will be performed in compliance with the conditions set forth in the ICH E6 on GCP as well as FDA regulation.

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

8.7 TEMPORARY HALT OF THE STUDY

The Sponsor may suspend the clinical study for any safety, ethical or administrative reason at any time.

If the Sponsor suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution/Sponsor should promptly inform the IRB(s)/IEC(s) and FDA and provide the IRB(s)/IEC(s) and FDA a detailed written explanation of the suspension.

The investigator, IRB(s) or FDA may suspend participation at the study sites for which they are responsible. In this case, the investigator should inform the institution, where applicable, and the investigator/institution should promptly inform the Sponsor and the IRB(s)/IEC(s) and should provide the Sponsor and the IRB(s)/IEC(s) a detailed written explanation of the suspension.

If the IRB(s)/IEC(s) suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable, and the investigator/institution should promptly notify the Sponsor and provide the Sponsor with a detailed written explanation of the suspension.

As per 21 CFR 312.42, the FDA may place a study on clinical hold. When a study is placed on clinical hold, participants may not be given the IMP and no new participant may be recruited to the study and placed on the investigational drug. Participants already in the study should be taken off therapy involving IMP unless specifically permitted by FDA in the interest of participant safety.

As per 21 CFR 312.45, if no participant is entered into clinical study for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the Sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the Sponsor shall have 30 days to respond as to why the IND should continue to remain active.

As per 21 CRF 321.44, an IND that remains on inactive status for 5 years or more may be terminated.

When a temporarily halted clinical study or in case of inactive status, the Sponsor will inform all involved investigators.

The restart of the clinical study following a temporary halt shall be deemed to be a substantial modification containing the proposed general investigational plan for the coming year and appropriate protocols.

Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment.

As per 21 CFR 312.45, the clinical study under an IND on inactive status may only resume:

- 30 days after FDA receives the protocol amendment, unless FDA notifies the Sponsor that the investigations described in the amendment are subject to a clinical hold
- or on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

8.8 END OF THE STUDY

The study will close when all participants have completed their last visit.

The study completion (US Clinical Trial Registry definition) is defined as the final date on which data is expected to be collected, *i.e.,* the date of the last visit of the last participant in the study.

The Sponsor will notify each IRB, FDA and all involved investigator sites concerned of the end of a clinical study.

Per the-ICH E6 R2-GCP, whether the trial is completed or prematurely terminated, the Sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

According to 21 CFR 312.64, upon study completion, the investigator will shortly provide the Sponsor and the IRB with final reports and summaries.

8.9 CONFIDENTIALITY OF THE IDENTITY OF PARTICIPATING PATIENTS

All study findings and documents will be regarded as confidential. The investigator and site staff must not disclose such information without prior written approval from the Sponsor.

The confidentiality of the identity of participating participants must be maintained.

Participants will be identified on e-CRFs and other documents by their participant number, and their year of birth and will not be identified by name, initials, or date of birth.

The e-CRFs number will identify all participants' collected data and their identity will remain unknown. The investigator is responsible for keeping a code list, which makes it possible to link participants assigned number to their name. This will be kept in a safe place to ensure that in case of emergency participants can be identified and contacted.

Documents that identify the participant (e.g., the signed ICF) must be maintained in confidence by the investigator and not be supplied to the Sponsor. If the participant's name appears on any other document (e.g., pathologist report), it must be removed before a copy of the document is supplied to the Sponsor. Participants will be told that representatives of the Sponsor or the Sponsor's representative, IRB(s), or FDA may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator must provide the Sponsor with complete test results and all data derived from the study. Only the Sponsor may make information obtained during the study available to physicians or regulatory agencies, except as required by regulation. Further details regarding confidentiality are provided in Section 9.4.3.

8.10 SUBJECTS/PATIENTS COMPENSATION

Patient compensation can be defined due to the constraints required by the study design, in the country where it is authorized by the IEC/IRB.

8.11 SUBMISSION OF THE STUDY RESULTS

In accordance with international standards, the Sponsor will submit to investigators involved, IRB(s) and FDA a summary of CSR study within one year from the end of the clinical study.

The participant may request to the investigator the overall summary of the results of the clinical study.

8.12 LIABILITY AND INSURANCE

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 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 study are governed by the applicable law.

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

9 STUDY MONITORING AND AUDITING

9.1 RESPONSIBILITIES OF THE SPONSOR

The Sponsor directly or through CROs is responsible for selecting qualified investigator(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the study.

The Sponsor will remind the investigator of his/her responsibilities and procedures for ensuring adequate and correct documentation.

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

The Sponsor or CROs will nominate a suitably trained person or persons to monitor the study and to liaise with the investigator.

The Sponsor and CROs will be responsible for ensuring that the clinical study is conducted in accordance with the CSP, ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the IMP, and for complying with the local regulations applicable to clinical studies.

9.2 RESPONSIBILITIES OF THE INVESTIGATOR

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

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

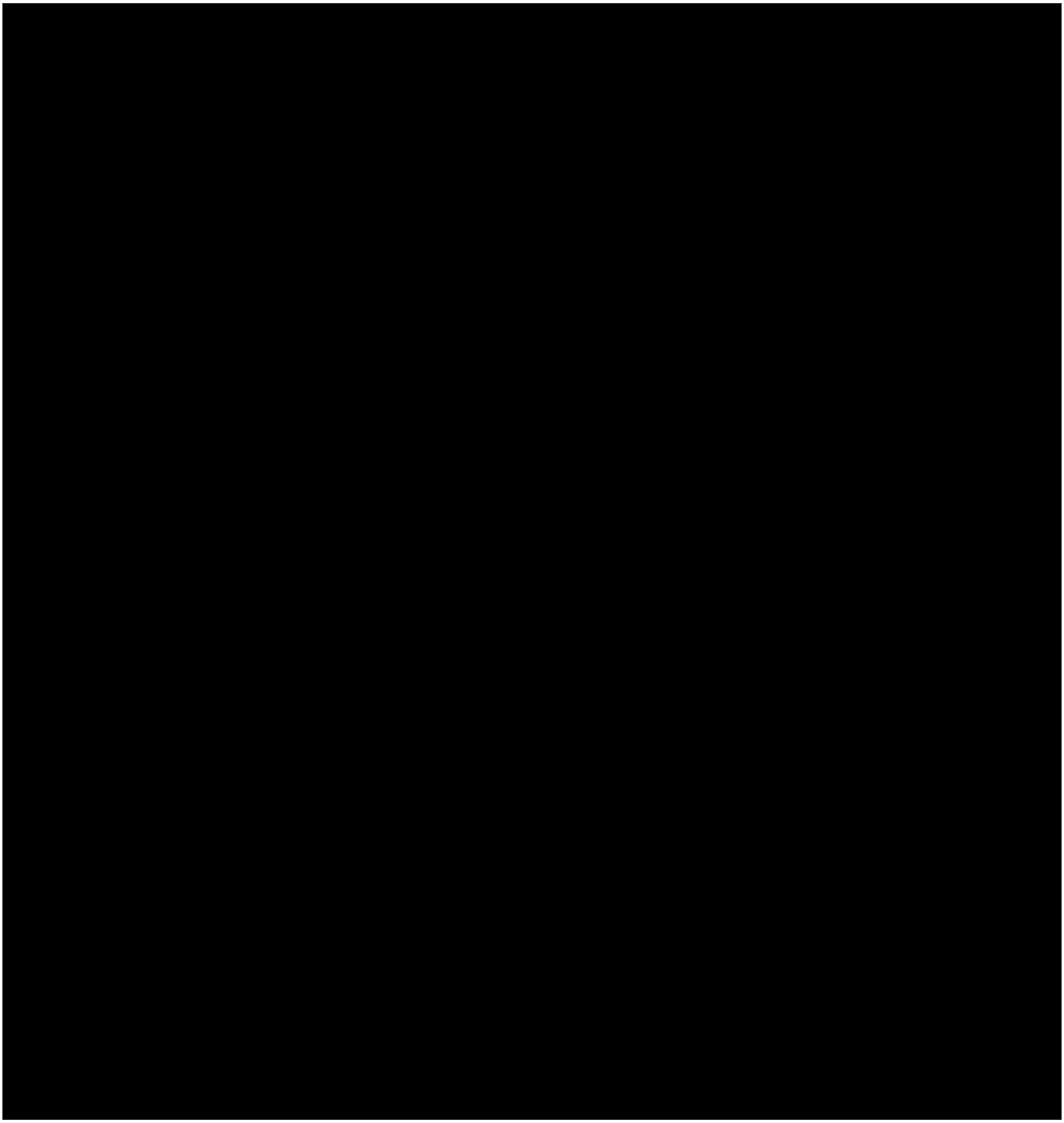
The investigator will conduct the study according to the approved CSP and in accordance with the Sponsor's guidelines and all applicable federal government codes, acts, and regulations, GCP requirements and ICH guidance E6 (R2) on GCP. It includes, but are not limited to:

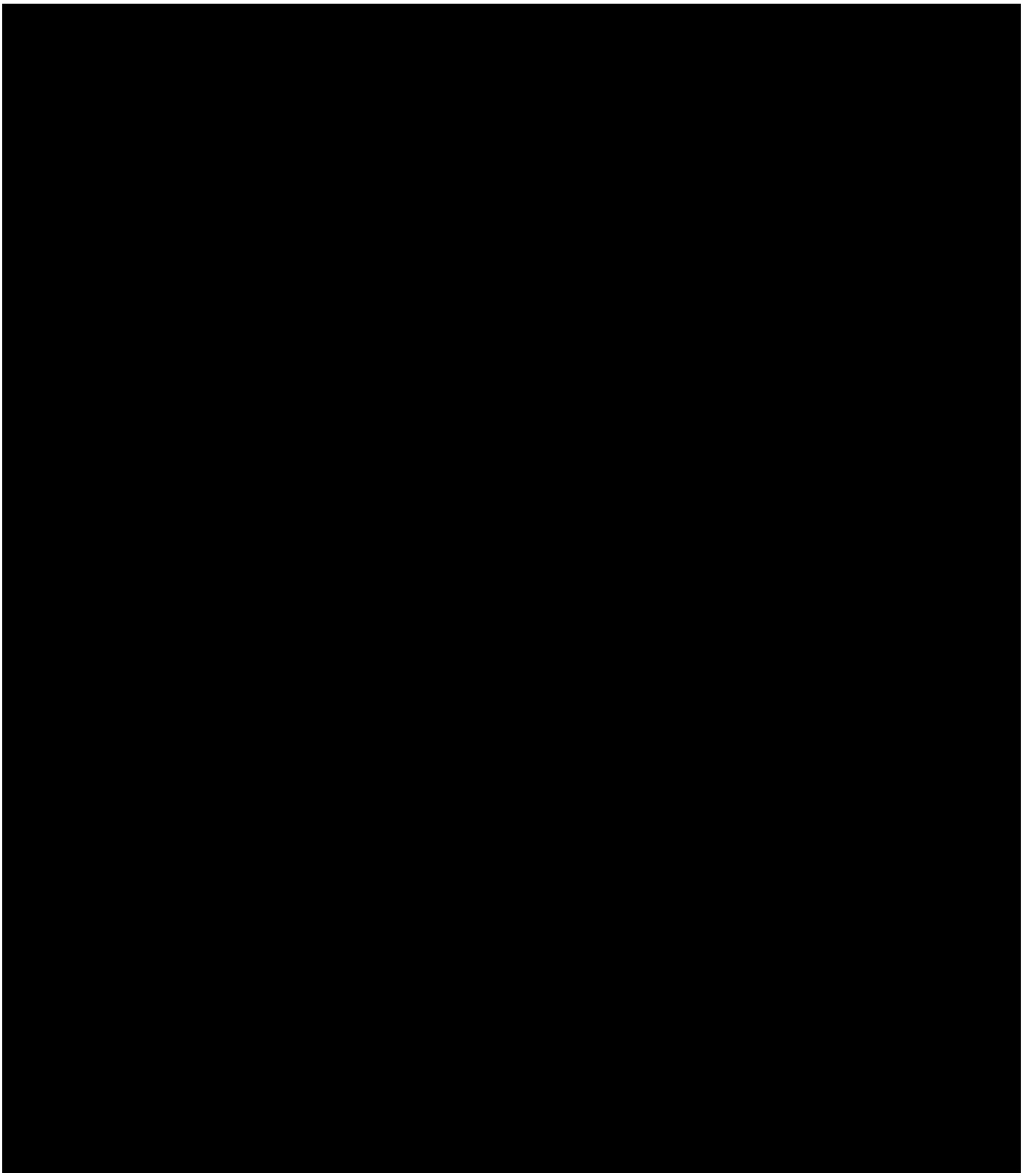
- Submission of the CSP, consent document(s), advertising text (if applicable) and other study document as requested by the IRB to a duly constituted IRB for approval and acquisition of written approval for each, prior to the site study initiation
- The investigator must have read and understood the information contained in the investigator's brochure, including the potential risks and side effects of the IMP
- Information of any potential participants that the IMP is being used for investigational purposes and obtention of a written consent document previously approved by the IRB prior to entry into the study or prior to any study procedures for all participants by ensuring that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met
- Maintain appropriate medical and research records for this study in compliance with ICH E6 (R2) GCP Sections 1.51, 1.52 and 4.9.0 and any other regulatory and institutional requirements for the protection of participants confidentiality
- Documentation and explanation of protocol deviations

- Submission of any proposed change in or deviation from the to the IRB, as required. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical study or the participants' rights, IRB approval must be obtained prior to implementation. IRB will be notified regarding changes that do not involve risk or affect the validity of the study or the participants' rights
- Submission of reports, to the IRB and Sponsor
- Permission to allow the Sponsor, the IRB, the FDA, or other regulatory agencies to monitor, audit, and inspect study facilities and pertinent records, including source data and documents, at reasonable times and in a reasonable manner that ensures participant confidentiality.

The investigator will cooperate with the Sponsor and CROs to monitor or supervise the conduct of the study.

9.3 STUDY MONITORING - SOURCE DATA VERIFICATION (SDV)





9.3.2 electronic case-report-form (e-CRF)

The e-CRF is used to convey data collected in the performance of this study.

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

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

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

The investigator is responsible for ensuring that data are properly recorded on each patient's e-CRF and related documents. The investigator is responsible for the punctuality, completeness, consistency, and accuracy of e-CRF. The e-CRF and source data will be retained by the investigator for data verification at each scheduled monitoring visit.

An investigator should personally sign the e-CRFs (as indicated in the case report forms) to ensure that the observations and findings are recorded on the e-CRFs correctly and completely.

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.

9.3.3 Source data verification, Monitoring/Data Audits

One of the primary responsibilities of monitoring is the review of source documentation (SDR =Source Data Review) to check quality of source, review protocol 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, ICH GCPs). 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 randomized into the study and that the information is listed in the source documents.

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

Source Data Verification (SDV) will be recorded in e-CRF and SAE/pregnancy related documents, consisting in a comparison of the source documentation and other records relevant to the study with the e-CRF. The SDV will ensure the data are Attributable, Legible, Contemporaneous, Original and Accurate (ALCOACCEA guiding principles).

Monitoring procedures developed by Laboratoires THÉA/CRO will be followed in order to comply with the CSP, ICH E6 (GCP guideline) and FDA regulation. Monitoring activities will be detailed in a Clinical Monitoring Plan.

On-site and/or remote checking of the e-CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

- medical questions concerning patients' safety
- verification of data from source documentation
- possible e-CRFs corrections and queries resolution
- IMPs questions.

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

Some monitoring activities will be performed remotely and will require investigator(s) and site staff availability: these activities included but are not limited to e-CRF completion and clarification, discussion about open issue/deviation, IMP question.

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

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 study 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 study is being carried out or to medical ethics.

9.3.4 On-site Audits/Regulatory inspection

Competent Authorities, 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 study may be subjected to auditing by representatives of the Sponsor and/or to inspection(s) by authorized representatives of local and/or foreign Competent Authorities. In case of an audit or inspection, the Investigator will be informed in advance.

9.4 DATA PROCESSING

9.4.1 Data collection and processing

Laboratoires THÉA, as Sponsor of the study is committed to protecting the privacy and security of personal data processed for the purposes of the study under the conditions defined below:

- **Compliance with the applicable laws or regulations:**

Laboratoires THÉA is committed to comply with applicable law regarding the processing of personal information and any other applicable law or regulation related to the protection of personal information.

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

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 information for the realization of the study.

In particular, the patients are informed by the Investigator during the delivery of the ICF, where all the mandatory information regarding the processing of their personal data 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, may have the right, under the conditions and within the limits provided by the regulations, to access, correct, or delete their personnel information.

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.

9.4.2 Record Retention

The investigator must retain the patient identification code for at least 25 years after completion or discontinuation of the study.

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 25 years, to meet the Sponsor regulatory local requirements.

The investigator must produce study documentation or supply copies thereof to Sponsor, its designee or to Competent Authorities upon request, while ensuring patient confidentiality at all times.

9.4.3 Confidentiality statement

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the IMP, 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 study 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 study.

9.4.4 Publication policy

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

Laboratoires THÉA will prepare a final CSR.

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. An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with Laboratoires THÉA in advance.