Pharmacodynamics of Investigational Medicinal Product (IMP) 08P2002F0 (Fixed dose combination of 0.34 % tropicamide and 2.5 % phenylephrine hydrochloride, eye drop Solution), a new ophthalmic mydriatic solution in healthy volunteers.

SOLMYD-PD
Clinical study protocol: UP-CLI-2023-01
Version 3.0 – 24 JUN 2025

Sponsor	**UNITHER PHARMACEUTICALS** 3-5 rue Saint-Georges 75009 Paris France
Test product	0.34 % tropicamide / 2.5 % phenylephrine hydrochloride (Compound number: 08P2002F0 "SLGL")
Development Phase	I/II integrated
EU CT number	2024-517456-35-00
Contract Research Organisation	**BECRO Ltd,** 7 Panos St, 41222 Larissa - Greece

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information: No use or disclosure outside UNITHER Pharmaceuticals is permitted without prior written authorization from UNITHER Pharmaceuticals.

PROTOCOL: SUMMARY OF CHANGE

Version number	Date	Changes from previous version
1.0	20 NOV 2024	Initial version
2.0	18 MAY 2025	Amendment 1 (before initial authorization)
3.0	24 JUN 2025	Amendment 2 (not substantial)

Amendment 02: 24 JUN 2025

Section # and Name	Description of Change	Brief rational if applicable
Cover page (page 1) Synopsis Study Objective	Trial phase was modified from Phase II to Phase I/II integrated	Condition required by competent authority with the study authorization
10.1-Reference Safety Information Document	To refer only to Section 4.8 of the comparator SmPC, as RSI for the comparator.	Condition required by competent authority with the study authorization

Amendment 01: 18 MAY 2025

Section # and Name	Description of Change	Brief rational if applicable
1-Synopsis	Implementation of the modification made in the protocol	Not applicable
2-Scheduled of Assessment	Addition of the pregnancy test, and study follow-up phone call	To correct a protocol discrepancy
3.3-Dose justification	Addition of a specific dose justification for the test IMP	To better justify the dosage
5.1-Study design	Addition of the study follow-up phone call in the design	To improve the safety assessment
5.2 5.2 Description of the measures to be taken to minimize or avoid bias, including Randomization and Masking	Modification of section title and clarification	To clarify the section
5.3-Emergency un-masking	Addition a procedure for emergency unbinding in the Protocol.	To clarify the process in case of unblinding by the masked-investigator
6.3.1-Inclusion criteria	Modification of inclusion criteria 3: Contraception	To comply with the CTFG recommendations for possible

	method to be used has been modified to highly effective contraception	categorization for IMPs with possible human teratogenicity/fetotoxicity (based on comparator SmPC data)
6.3.2-Exclusion criteria	Modification of exclusion criteria 7, Addition of exclusion criteria 20, 21, 22, 23, and modification of exclusion	To correct a discrepancy of protocol between two different sections, and to include information from the interaction section of the protocol to the exclusion criteria as specific contraindicated medications,
6.4.4-Contraceptive regimen throughout the study	Contraception method to be used has been modified to highly effective contraception	To comply with the CTFG recommendations for possible categorization for IMPs with possible human teratogenicity/fetotoxicity (based on comparator SmPC data)
7- Subject discontinuation of treatment and discontinuation or withdrawal from trial	Addition of a section relative to the discontinuation of treatment and discontinuation or withdrawal from trial, and deletion of previous section 8.5 relative to	To describe in detail the discontinuation criteria for study subjects (either from treatment or from the trial) and procedures for collection of data relating to withdrawn subjects
10.1-Reference Safety Information Document	Specification has been added regarding which section of the SmPC of comparator will be used as RSI	To include in the Protocol information on which part of the SmPc comparator is to be used as reference safety information for this clinical trial
10.Safety including section 10.4-Collection, assessment and reporting of AE, ADR and SAE	Modification of the section	To align protocol section “Collection, assessment and reporting of AE, ADR and SAE with requirements set in Articles 41 and 42, ANNEX I and ANNEX III of Clinical Trials REGULATION (EU) No 536/2014

I. SIGNATURES

INVESTIGATORS' AGREEMENT FOR INTERVENTIONAL CLINICAL STUDY

STUDY TITLE: Pharmacodynamics of IMP 08P2002F0 (Fixed dose combination of 0.34% tropicamide and 2.5% phenylephrine hydrochloride, eye drop, Solution) a new ophthalmic mydriatic solution in healthy volunteers.

STUDY CODE: UP-CLI-2023-01

EU CT Number: 2024-517456-35-00

I acknowledge that I have read the above named Protocol and I agree to carry out all of its terms in accordance with applicable regulations and law, to follow ICH Good Clinical Practice (GCP) guidelines for good clinical practice, the Declaration of Helsinki by the World Medical Association and all current local rules and regulations on the conduct of clinical trials with human subjects, to obtain approval from the Institutional Review Board (IRB)/ Independent Ethic Committee (IEC) prior to implementation, to allow direct access to source documents, and agree to inspection by auditors from Unither Pharmaceuticals and regulatory authorities, as required by ICH GCP.

I understand that any factual information not published is kept in strict confidentiality. Such information includes the protocol, the Case Report Form (CRF) and other scientific data.

PRINCIPAL INVESTIGATOR (PI)

_____

Signature

Name:

Date: _____
(dd-mmm-yyyy)

SPONSOR'S STUDY AND PROTOCOL APPROVAL

STUDY TITLE: Pharmacodynamics of IMP 08P2002F0 (Fixed dose combination of 0.34% tropicamide and 2.5% phenylephrine hydrochloride, eye drop, Solution) a new ophthalmic mydriatic solution in healthy volunteers.

STUDY CODE: UP-CLI-2023-01
EU CT Number: 2024-517456-35-00

UNITHER Pharmaceutical
3-5 Rue Saint-Georges
75009 Paris
France

Sponsor's Representative

_____
Signature

Name: [redacted]

Date: _____
(dd-mmm-yyyy)

PROTOCOL AUTHORS:



Signature:

Date:
(dd-mmm-yyyy)

II. Contact Details of Key Personnel

CRO BECRO Ltd	[redacted]
Clinical Research Contact:	[redacted]

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BPM	Beats per Minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
DB	Database
DPO	Data Protection Officer
ECG	Electrocardiogram
EMA	European Medicines Agency
EOF	National organization of medecine
EU	European Union
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
h	Hour
HCl	Hydrochloride
IEC	Independent Ethic Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instruction For Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
kg	kilogram
L	liter
ln	Neperian log transformation
SLGL	

MAOI	Monoamine oxidase inhibitors
MEDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
min	minute
mL	milliliter
mmHg	millimeter of mercury
NEC	National Ethics Committee
OTC	Over the counter
pH	the logarithm, on the base 10, of the reciprocal of the hydrogen ion concentration
PI	Principal Investigator
PP	per-protocol
QA	Quality Assurance
SAP	Statistical Analytical Plan
SOC	System Organ Classification
SOP	Standard Operating Procedure
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
US-FDA	Food and Drug Administration of the United States of America

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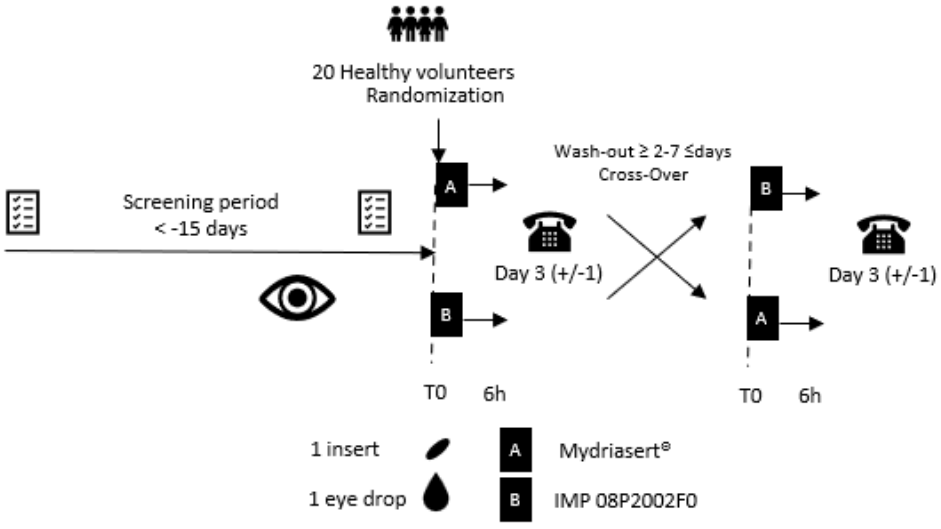
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1 PROTOCOL SYNOPSIS

Title	Pharmacodynamics of Investigational Medicinal Product (IMP) 08P2002F0 (Fixed dose combination of 0.34 % tropicamide and 2.5 % phenylephrine hydrochloride, eye drop, Solution) a new ophthalmic mydriatic solution in healthy volunteers.
EU CT number	2024-517456-35-00
Protocol code	UP-CLI-2023-01
Phase	Phase I/II integrated
Study Objective	The objective of this phase I/II study is to explore pharmacodynamic effects and safety of IMP 08P2002F0 for dilation of the pupil, a solution combining two mydriatic agents tropicamide and phenylephrine hydrochloride at the concentrations of 0.34% and 2.5% respectively, versus Mydriasert®.
Design	Open-label, Observer-masked, active-controlled, randomized cross-over phase I/II study in healthy volunteers. 
Treatments	*Test product:* IMP 08P2002F0: Fixed combination of 0.34 % tropicamide and 2.5 % phenylephrine Hydrochloride (HCl) Eye drop Solution. *Reference product:* Mydriasert® insert (0.28 mg tropicamide and 5.4 mg phenylephrine hydrochloride)
Subjects	20 healthy volunteers (10 in each sequence) of both genders that comply with the inclusion criteria and none of the exclusion criteria.

Inclusion-exclusion criteria	***Inclusion Criteria*** ***A Subject will be eligible for inclusion in this study only if all the following criteria are met:*** **1.** Healthy volunteers of both genders, aged ≥18 at the time of signing the informed consent. **2.** Healthy volunteers are declared healthy based on medical history, physical examination, ophthalmological examination, Electrocardiogram (ECG), within the stated normal range; a participant with a clinical abnormality or laboratory parameter(s) outside the reference range may be included if the investigator agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or interpretation.. **3.** Females who participate in the study, that are at reproductive age (1) agree to undergo pregnancy tests and to use a highly effective birth control method (2) during the study. 1) A woman is considered to be with childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). 2) The following are considered as highly effective birth control methods : Established use of oral, intravaginal or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; established use of oral, injected, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine hormone-releasing system or placement of an intrauterine device; bilateral tubal occlusion; vasectomised partner; true abstinence. **4.** Subjects that, in the opinion of the investigator, are able to understand and comply with the study procedures and protocol restrictions. **5.** Subjects who have read, signed and dated the Informed Consent Form (ICF) prior to the study initiation. ***Exclusion Criteria*** **1.** Hypersensitivity to the active substances or to the excipients or related class of the medicinal product. Serious hypersensitivity reactions include angioedema, anaphylaxis and exfoliative skin conditions including Stevens-Johnson syndrome. **2.** Clinically significant illness or surgery within four weeks prior IMP administration. **3.** Clinically significant ECG abnormalities or vital sign abnormalities (seated systolic blood pressure < 90 or >140 mmHg, seated diastolic blood pressure < 50 or > 90 mmHg or heart rate less than 50 or over 100 bpm) at screening.

	4. History or presence of any clinically significant cardiovascular, pulmonary, hepatobiliary, renal, haematological, gastrointestinal, endocrinologic, immunologic, dermatologic, neurological, psychiatric, metabolic, musculoskeletal, malignant disease or eye disorders as glaucoma or a family history of glaucoma. **5.** Clinically significant abnormal laboratory values. **6.** Unwilling to discontinue use of contact lenses on the day of a treatment visit. **7.** Current active eye disease (i.e. any disease for which topical or systemic ophthalmic medication is necessary). In case of historical eye disease, topical or systemic ophthalmic medication should have been stopped for at least one month before the study. **8.** Pupillary abnormalities (irregular, very dark iris, iris synechiae, eye movement disorder (e.g. Nystagmus, etc.), dacryocystitis and all other pathologies of tears drainage system. **9.** Use of any ophthalmic medication except unpreserved artificial tears on the day of a treatment visit. **10.** History of inflammatory ocular disease (e.g. iritis, uveitis, herpetic keratitis). **11.** History of ocular trauma, infection or inflammation within the last 3 months. **12.** Ocular surgery or laser treatment of any kind in the study eye within 3 months. **13.** Irregularly-shaped pupil secondary to ocular trauma, intraocular surgery or congenital defect. **14.** History of neurogenic pupil disorder (e.g. Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.). **15.** History of iris surgery of any kind (e.g. iridotomy, iridectomy, coreoplasty). **16.** History of previous corneal surgery; iris atrophy, traumatic mydriasis or angle recession, chronic or acute uveitis. **17.** Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration and superficial punctuate keratitis).

	18. Pseudoexfoliation, exfoliative syndrome. **19.** History of closed-angle glaucoma. **20.** Subjects with narrow angle prone to glaucoma precipitated by mydriatics **21.** Subject undergoing treatment identified as potentially interacting with the IMP, including antidepressant drugs, beta-blockers, other indirect sympathomimetics, alpha sympathomimetics (oral and/or nasal routes), dopaminergic ergot alkaloids, ergot alkaloid vasoconstrictors, selective MAOI-A, linezolid, and halogenated volatile anesthetics. **22.** Subject planning to receive an MAOI within 3 weeks following the end of the study. **23.** Subjects who have received non-selective monoamine oxidase inhibitors (MAOIs) within the last 15 days **24.** History of significant alcohol or drug abuse within one year prior to the screening visit. **25.** Regular use of alcohol within six months prior to screening visit (more than 14 alcohol units per week) [1 Unit =150 ml of wine, 360 ml of beer, or 45 ml of 40 % alcohol]. **26.** Inability to abstain from alcohol for the duration of study period. **27.** Positive results for drugs of abuse (barbiturates, marijuana, opioids, benzodiazepines and methadone) in saliva before each administration. **28.** Positive alcohol breath test before each administration. **29.** Use of soft drugs (such as marijuana) within three months prior to screening or hard drugs such as crack, cocaine or heroin within one year prior to screening visit. **30.** Participation in another clinical trial simultaneously. **31.** Breastfeeding women. **32.** Positive pregnancy test at screening. **33.** Females of reproductive age that had sexual intercourse with a non-sterile male partner without highly effective contraception within 14 days prior to drug administration.

Subject Selection Procedures	Demographic data, body measurements, medical history, medication history, physical examination, ophthalmic examination, vital signs, ECG, pregnancy urine test
Administration	*Test product*: IMP 08P2002F0: 1 eye drop in the study eye. Rinsing with NaCl 0.9 % will be performed 30 min after instillation *Reference product:* Mydriasert® insert: 1 insert will be kept onto the study eye for one hour. Then Insert is retrieved and rinsing with NaCl 0.9 % will be performed after retrieval of insert (performed after a contact time of 60 min). Insert will be placed into and removed from the lower conjunctiva fornix of the eye using sterile forceps.
Washout period	At least 2 days and maximum 7 days (included) i.e. ≥ 2 days up to ≤ 7 days
Study Duration per subject	Duration for each subject from screening to follow-up: 28 days
Examinations During the Study	urine pregnancy test for pre-menopausal female subjects prior to each administration.
Study Plan	Screening-Visit 1 (V1): Potentially eligible healthy volunteers after signing the Informed Consent Form (ICF) will be screened on Visit 1 (Screening). From signature of informed consent to first IMP intake, the screening tests should be performed, and their results checked by the Investigator within a period of 15 days before the first IMP administration (Period 1). Period 1: Healthy volunteers who meet all eligibility criteria will be randomized to sequence 1 (Test followed by Reference) or Sequence 2 (Reference followed by Test). The eye to be treated (study eye) will be also randomized. Baseline data of pupil diameter are obtained right before or within 10 min before IMP administration. Then, the first administration of IMP according to the assigned sequence (i.e. Test for sequence 1 and Reference for sequence 2) will be administered. Rinsing will be performed with NaCl 0.9 % 30 min after instillation of IMP 08P2002F0, and right after retrieval of insert (performed after a contact time of 60 min).

	Subjects will be followed 6 hours after the IMP administration. Study ophthalmic assessments include slit lamp examination and pupil diameter measurement. Pupil diameter measurement will be performed at 10 min (± 2 min), 20 min (± 2 min), 30 min (± 2 min), 45 min (± 5 min), 60 min (± 5 min), 1 h 15 (± 5 min), 1 h 30 (± 10 min), 2 h (± 10 min), 2 h 30 (± 10 min), 3 h (± 10 min), 3 h 30 (± 10 min), 4 h (± 10 min), 4 h 30 (± 10 min), 5 h (± 10 min), 6 h (± 10 min) post-administration. Discomfort questionnaire will be answered by subject at 10 min (± 2 min), 30 min (± 2 min), 60 min (± 5 min), 2 h (± 10 min), and 6 h (± 10 min) post-administration. A follow-up call will be performed 3 days (+/-1) after study administration Period 2: After a washout period of at least 2 days and maximum 7 days (included), the second IMP administration will be performed. Baseline data of pupil diameter are obtained right before or within 10 min before IMP administration. The subjects will be administered the second IMP according to the assigned sequence (i.e. Reference for sequence 1 and Test for sequence 2). Rinsing will be performed with NaCl 0.9 % 30 min after instillation of IMP 08P2002F0, and after retrieval of insert (performed after a contact time of 60 min). Subjects will be followed 6 hours after the IMP administration. Pupil diameter measurement will be performed at 10 min (± 2 min), 20 min (± 2 min), 30 min (± 2 min), 45 min (± 5 min), 60 min (± 5 min), 1 h 15 (± 5 min), 1 h 30 (± 10 min), 2 h (± 10 min), 2 h 30 (± 10 min), 3 h (± 10 min), 3 h 30 (± 10 min), 4 h (± 10 min), 4 h 30 (± 10 min), 5 h (± 10 min), 6 h (± 10 min) post-administration. Discomfort questionnaire will be answered by subject at 10 min (± 2 min), 30 min (± 2 min), 60 min (± 5 min), 2 h (± 10 min), and 6 h (± 10 min) post-administration. A follow-up call will be performed 3 days (+/- 1) after study administration. The study for each subject will be terminated after the follow-up call of the second period.
Safety Data	Safety evaluation will be based on the assessment of the adverse events and the vital signs.

Primary objective	Change in pupil diameter at 60 min from the time of first dose versus baseline, as measured with photo (central reading)
Second efficacy objectives:	• Time to obtain sufficient mydriasis. (defined as pupil diameter of 7 mm) • Proportion of eyes achieving pupil diameter of 6.0 mm or greater throughout the 6 hours, at 30 min, at 1 h, at 2 h. • Proportion of eyes achieving pupil diameter of 7.0 mm or greater throughout the 6 hours, at 30 min, at 1 h, at 2 h. • Time from baseline to maximal pupil dilation • Change in pupil diameter at other timepoints (10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 h) • Pupil size measured at 10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 hours. • Distribution of pupil diameters at 10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 hours. • Subject discomfort at 10 min, 30 min, 60 min, 1 h 30, 2 h, and 6 h post-administration. • Percent of Subjects' Study Eyes with Pupil Diameter Returning to Baseline [Time Frame: throughout the 6 hours, at 3 h, 4 h, 5 h, 6 h] • Percentage of subjects' study eyes returning to less than or equal to 0.2 mm from baseline pupil diameter [Time Frame: throughout the 6 hours, at 3 h, 4 h, 5 h, 6 h].
Safety objective	• Occurrence of Adverse events • Ocular symptoms other than mydriasis
Statistical Analysis	*Sample Size:* No prospective calculations of statistical power are made as this study is being conducted as a preliminary study. A total of 20 healthy volunteers (i.e. 10 subjects in each sequence) of both genders will be included in the study and treated with the investigational products.
	Data Analysis: The primary objective is to evaluate the efficacy of IMP 08P2002F0 (Test, T) for dilation of the pupil compared to Mydriasert® (Reference, R). The primary endpoint (change in pupil diameter at 60 min from the time of first dose versus baseline) is analyzed using a general linear model for a cross-over design.

	The secondary endpoints (corresponding to secondary efficacy objectives) will be analyzed with general linear models, or paired t-test, for continues variables and chi-squared test for categorical variables. A result is considered significant at $p < 0.05$. The statistical analysis will be done in full agreement with the International Council for Harmonization (ICH) Topic E9, Statistical Principles for Clinical Trials. Detailed description of analyses will be provided in Statistical Analysis Plan approved before Database (DB) lock. Safety Data: Safety will be assessed during the study using reporting of adverse events (AEs). All AEs, Serious Adverse Event (SAE), non-serious AEs-related to IMP, or AE leading to interruption and discontinuation of IMP will be described. Number of events, number and percentage of subjects with at least one event and incidence rate, AEs intensity and severity will be also described.
Subject Population Analysis	*Safety population*: The safety population comprises all subjects who have received at least one application of the Test or Reference. *ITT population:* The intent-to-treat (ITT) population includes all randomized subjects who had at least one post baseline assessment. *PP population*: The per-protocol (PP) population includes all subjects of the ITT population without major protocol violations, who were compliant subjects, and did not withdraw from the study.

2 SCHEDULE OF ASSESSMENT

Table 1: study flowchart

Procedures	Screening visit	Period 1	Washout	Period 2
Study days	**-15 to 0**	**Day 1**		**Days 4 to max Days 9**
Informed consent signature	X		**≥ 2 days & ≤ 7 days**	
Demographic data	X			
Medical and medication history	X			
Physical examination	X			
Body measurements	X			
Vital signs (blood pressure, heart rate, temperature)	X	X		X
ECG	X			
Pregnancy test (in urine) before administration	X	X		X
Randomization		⊗		
Inclusion criteria	X	X		
Exclusion criteria	X	X		
Ocular history	X			
Slit lamp examination	X	⊗		⊗
Study drug administration		⊗		⊗
Pupil diameter photography		⊗		⊗
Pupil diameter measurement on photography (performed by a masked-investigator)		X		X
Pupillary light reflex		X		X
Discomfort questionnaire		⊗		⊗
Follow-up call (3 days (+/- 1h) after study administration		⊗		⊗
Prior and Concomitant Medications	X	X		X
Adverse Events	X	X		X

⊗ Non-Masked Investigator
X Masked Investigator

Table 2: Timing of Assessment on day 1 during treatment periods I, II

	Within –10 min	0 min	10 min (± 2)	20 min (± 2)	30 min (± 2)	45 min (± 5)	60 min (± 5)	1h15 (± 5)	1h30 (± 10)	2h00 (± 10)	2h30 (± 10)	3h00 (± 10)	3h30 (± 10)	4h00 (± 10)	4h30 (± 10)	5h00 (± 10)	6h00 (± 10)
Administration of Insert		⊗															
Retrieval of insert followed by NaCl							⊗ NaCl										
Administration of study drug (IMP 08P2002F0)		⊗															
Rinse with NaCl for IMP 08P2002F0					⊗ NaCl												
Pupil measurement Method: photography	⊗		⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
Discomfort questionnaire			⊗		⊗		⊗			⊗							⊗

3 INTRODUCTION

3.1 Indication and Context

Mydriasis, or pupil dilation, is an important tool used extensively in ophthalmological clinical practice.

Efficient and stable mydriasis is necessary during many diagnostic and surgical procedures in ophthalmology such as fluorescein angiography, laser photocoagulation and cataract or retinal surgeries.

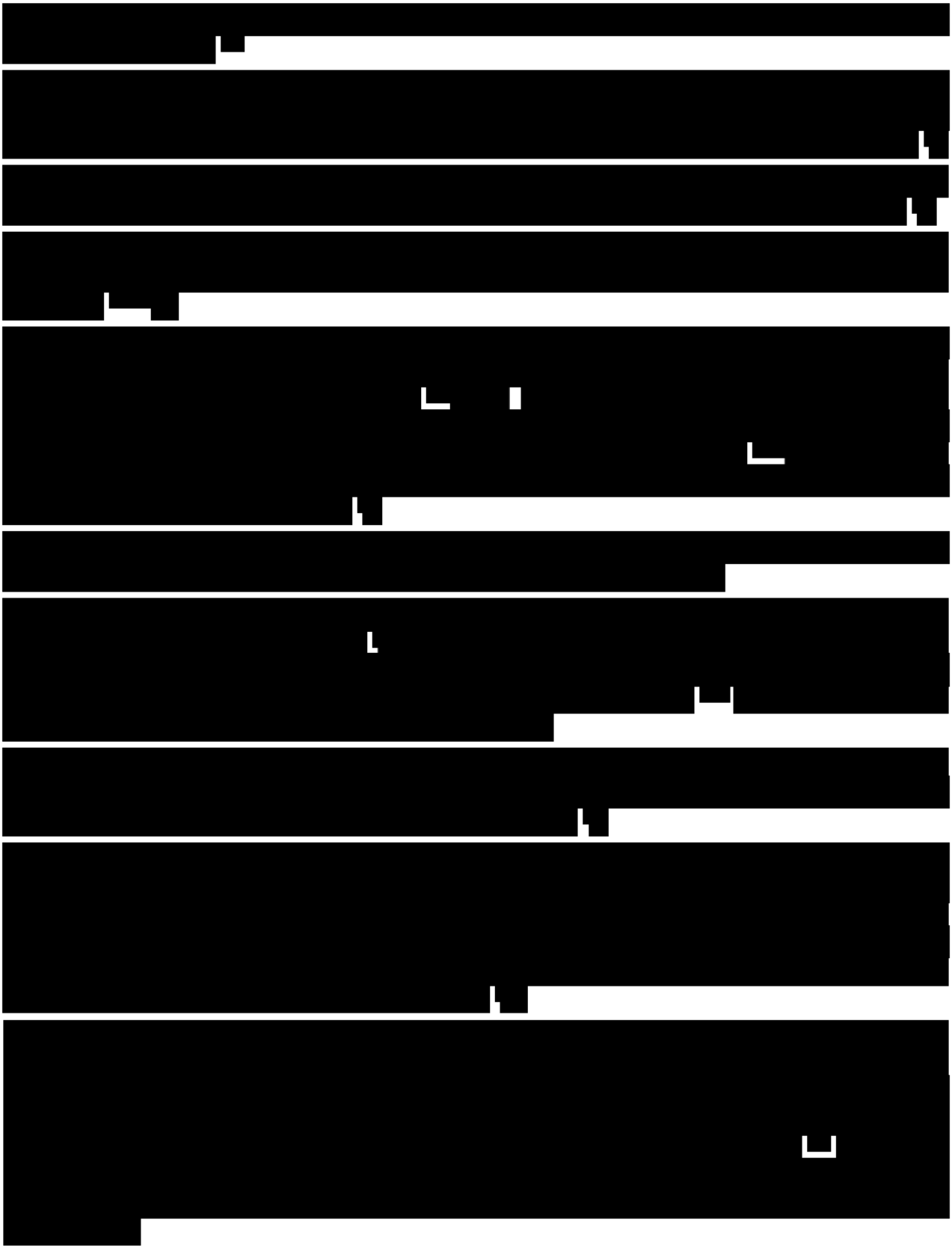
The duration of mydriasis necessary for the ophthalmic procedure can vary with a short mydriasis for disease diagnosis purposes (5 min can be enough), to a long mydriasis in case of complex situations for retinal surgery (until approximately 3 hours).

The quality of an intraocular examination depends on adequate pupil dilation. The ideal mydriatic should show a rapid onset of action, achieve adequate mydriasis, permit a quick recovery, and not cause discomfort or side effects [1]. Poor mydriasis can increase the risk of intraoperative complications during surgery [2].

The pupil is under the control of the autonomic nervous system. Parasympatholytic as well as sympathomimetic drugs have been used to dilate the pupil. The parasympathetic regulation dominates over the sympathetic effect in the control of the pupil [3]. Therefore, application of only the sympathomimetic drug is usually inadequate to sustain the pupil dilation in bright light during indirect ophthalmoscopy. parasympatholytic agents alone may also not provide sufficient pupil dilation. Combination of both drugs offers greater pupil dilation than single drug use [4].

3.2 Rational for tropicamide and phenylephrine HCl Fixed Drug Combination

[redacted]



[redacted]

3.3 Dose justification

One of the targets of this development was to propose an adequate mydriatic product for patients and healthcare professionals that is effective with only one instillation.

[redacted]

[redacted]

3.4 Non-Clinical and clinical Information

Non-clinical development

Non-clinical pharmacology and tolerance studies were performed in accordance with Good Laboratories practice. For more information, refer to the Investigator's Brochure.

Clinical development

No clinical study has been already performed with IMP 08P2002F0.

However, as tropicamide and phenylephrine have been used both as mono-component, or in combination for a long time, effects in human are known, and could be described based on literature.

Risks and benefits for IMP are detailed in section 10.2.3.

The investigator must become familiar with all sections of the Investigator's Brochure which will be provided by the Sponsor before the start of the study.

3.5 Rational of the study

The objective of this phase I/II study is to explore pharmacodynamic and safety of IMP 08P2002F0, a solution combining two mydriatic agents tropicamide and phenylephrine hydrochloride at the concentrations of 0.34 % and 2.5 % respectively, versus Mydriasert®.

3.6 Risk-benefit assessment

Participating in a pharmacodynamic study as healthy subject does not benefit immediately to the volunteers.

The risks a healthy volunteers would encounter from taking two doses, with a washout period of ≥ 2 days to ≤ 7 days, of Test Product and Reference Product in the approved content of phenylephrine HCl and tropicamide are reduced. If adverse events occur from the study drugs or study procedures, they are expected to be mild and minimal and within the commonly reported ones as described in the Investigator Brochure.

3.7 Discussion of Study Design

The sponsor, Unither Pharmaceuticals, has developed a new preservative free fixed dose combination of tropicamide 0.34 % and phenylephrine hydrochloride 2.5 % eye drop solution. This

product has the same combination of active substances as Mydriasert® insert but with notable differences compared to Mydriasert®. The reference medicinal product has already been granted a marketing authorisation in multiple countries in European Union (EU).

The purpose of conducting this phase I/II study is to explore pharmacodynamic and safety of IMP 08P2002F0, the new medicinal product of tropicamide 0.34 % and phenylephrine hydrocholoride 2.5 % compared to Mydriasert® insert.

The measuring time of 6 hours, over which pupil diameter will be measured, is judged to be sufficiently long to adequately describe the pharmacodynamic profile of phenylephrine HCl and tropicamide [14].

Phenylephrine HCl and tropicamide are well established substances.

4 STUDY OBJECTIVES AND ENDPOINTS

The objective of this pilot study is to explore pharmacodynamic and safety of IMP 08P2002F0, a solgel solution combining two mydriatic agents tropicamide and phenylephrine HCl at the concentrations of 0.34 % and 2.5 % respectively, versus Mydriasert®.

4.1 Primary objective/endpoint

The primary objective of this study is to evaluate the pharmacodynamic effect of IMP 08P2002F0 for dilation of the pupil as compared to Mydriasert®. The primary endpoint is the change in pupil diameter at 60 min from the time of first dose versus baseline, as measured with pupil photographs (central reading)

4.2 Secondary objectives/ Endpoints:

Other objectives of the study are to assess after single administration:

- Time to obtain sufficient mydriasis. (Defined as pupil diameter of 7.0 mm),
- Proportion of eyes achieving pupil diameter of 6.0 mm or greater throughout the 6 hours, at 30 min, at 1 h, at 2 h,
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater throughout the 6 hours, at 30 min, at 1 h, at 2 h,
- Time from baseline to maximal pupil dilation,
- Change in pupil diameter at other timepoints (10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 h),
- Pupil size measured at 10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 h
- Distribution of pupil diameters at 10 min, 20 min, 30 min, 45 min, 60 min, 1 h 15, 1 h 30, 2 h, 2 h 30, 3 h, 3 h 30, 4 h, 4 h 30, 5 h, 6 h.

- Subject discomfort at the following recording times: 10 min, 30 min, 60 min, 2 h, 6 h
- Percent of subjects' study eyes with Pupil Diameter Returning to Baseline [Time Frame: throughout the 6 hours, at 3 h, 4 h, 5°h and 6 h]
- Percentage of subjects' study eyes returning to less than or equal to 0.2 mm from baseline pupil diameter [Time Frame: throughout the 6 hours, at 3 h, 4 h, 5°h and 6 h].

4.3 Safety objective

Safety profile of IMP 08P2002F0 in comparison with Mydriasert®.

- Occurrence of Adverse events

  Ocular symptoms other than mydriasis

5 STUDY DESIGN AND DURATION

5.1 Study Design

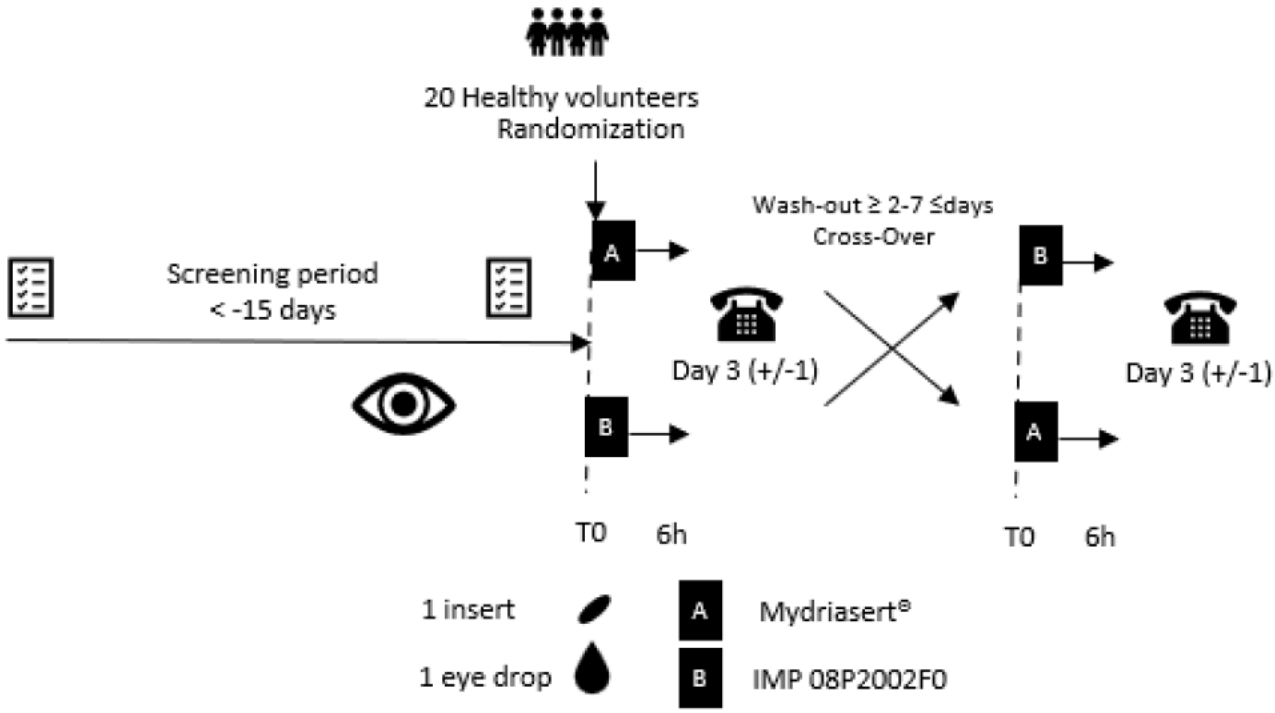


Figure 1 : study design

This will be a single dose, observer-masked, 2-period, 2-sequence (test product followed by reference product or reference product followed by test product), crossover design study in 20 healthy male and female subjects (i.e. 10 individuals in each sequence).

The order of administration of the studied products will be randomized. The eye to be treated will be also randomized. The study will be finished in two periods, during each of which a single administration will be conducted. The two periods will be separated by a washout period of at least 2 days and maximum 7 days (included) i.e. ≥ 2 days up to ≤ 7 days.

The subjects will be administered a single dose of either the test (1 eye drop) or the reference product (1 insert which will be kept onto the eye for one hour) after baseline measurements of ophthalmic examination (pupil diameter). The baseline measurements should be performed right before or within 10 minutes prior to IMP administration.

The study design can be described as follows:

	Period 1	**Period 2**
Sequence 1 (n=10)	Test product IMP 08P2002F0: Fixed combination of 0.34 % tropicamide and 2.5 % phenylephrine HCl eye drop solution	Reference product Mydriasert® insert (0.28 mg tropicamide and 5.4 mg phenylephrine hydrochloride)
Sequence 2 (n=10)	Reference product Mydriasert® insert (0.28 mg tropicamide and 5.4 mg phenylephrine hydrochloride)	Test product IMP 08P2002F0: Fixed combination of 0.34 % tropicamide and 2.5% phenylephrine HCl, eye drop solution

Table 3: Periods

5.2 Description of the measures to be taken to minimize or avoid bias, including Randomization and Masking

Each treatment will be administered to the subjects according to the randomization code yielded by BECRO Ltd. Subject randomization will take into account the study design, the sample size and the administration sequence. The subjects will be randomized in the two sequences in a balanced design. The personnel implicated with the study drug administration will be responsible for the compliance with the randomization scheme.

The clinical trial will be performed as single investigator-masked because of the differences in the pharmaceutical form of both drugs that makes a double-masked design impossible.

The clinical trial site will have masked and not-masked Investigators.

Not-masked investigator is responsible for clinical trial medication administration, pupil diameter photographs, examinations as indicated in the scheduled of assessment whereas the masked Investigator performs other examination and pupil diameter measurement.

Volunteers and non-masked staff should not disclose trial assignments to the masked evaluator; the treatment assignment records are unavailable to masked personnel.

The randomization code will not be accessible to the Investigator that will perform the clinical assessment until the clinical phase of the study has been finished.

5.3 Emergency un-masking

The code should not be broken for the masked investigator in charge of measuring the diameter on the photograph at any time. Medical emergencies should be handled, if possible, by the unmasked investigator following the subject during the visit at study site.

If an emergency unmasking becomes necessary for the masked investigator in case of his medical expertise is requested to handle the medical emergency or when it is a regulatory requirement; the investigator should notify the Sponsor, if possible, prior to being un-masked. In that case, the not-masked investigator who is following the subject during the visit, could communicate the "code".

The date, time and reason must be recorded in the patient's source documentation as well as in the CRF, and in any associated AE report.

6 SELECTION OF STUDY POPULATION

6.1 Sample Size

No prospective calculations of statistical power are made as this study is being conducted as a preliminary study.

A total of 20 healthy volunteers (i.e. 10 subjects in each sequence) of both genders will be included in the study and treated with the investigational products.

6.2 Selection of Study Population

Subject screening procedures will be performed within 15 days prior to first administration of study medication. Subject selection should only begin after voluntary agreement to sign and date a statement of Informed Consent (ICF), and before any study-related procedure is undertaken. The selection of the study population will be based on demographic data, medical history, medication history and the results of the physical and ophthalmic examination [slit lamp examination]. Subjects with medical history likely to significantly influence their pharmacodynamic response to the treatment will have to be excluded from the study.
Description of clinical measures and procedures applying to all periods is given in SCHEDULE OF ASSESSMENT

Table 1: study flowchart

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6.3 **Inclusion/Exclusion Criteria**

6.3.1 Inclusion Criteria

A Subject will be eligible for inclusion in this study only if all the following criteria are met:

1. Healthy volunteers of both genders, aged ≥ 18 at the time of signing the informed consent.

2. Healthy volunteers are declared healthy based on medical history, physical examination, ophthalmological examination, ECG, within the stated normal range; a participant with a clinical abnormality or laboratory parameter(s) outside the reference range may be included if the investigator agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or interpretation..

3. Females who participate in the study, that are at reproductive age (1) agree to undergo pregnancy tests and to use a highly effective birth control method (2) during the study.

   1) A woman is considered to be with childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   2) The following are considered as highly effective birth control methods : Established use of oral, intravaginal or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; established use of oral, injected, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine hormone-releasing system or placement of an intrauterine device; bilateral tubal occlusion; vasectomised partner; true abstinence.

4. Subjects that, in the opinion of the investigator, are able to understand and comply with the study procedures and protocol restrictions.

5. Subjects who have read, signed and dated the Informed Consent Form (ICF) prior to the study initiation.

6.3.2 Exclusion Criteria

Subjects with the following criteria will be considered as not eligible to enter in the study:

1. Hypersensitivity to the active substances or to the excipients or related class of the medicinal product. Serious hypersensitivity reactions include angioedema, anaphylaxis and exfoliative skin conditions including Stevens-Johnson syndrome

2. Clinically significant illness or surgery within four weeks prior the IMP administration.

3. Clinically significant ECG abnormalities or vital sign abnormalities (seated systolic blood pressure < 90 or > 140 mmHg, seated diastolic blood pressure < 50 or > 90 mmHg or heart rate less than 50 or over 100 bpm) at screening.

4. History or presence of any clinically significant cardiovascular, pulmonary, hepatobiliary, renal, haematological, gastrointestinal, endocrinologic, immunologic,

dermatologic, neurological, psychiatric, metabolic, musculoskeletal, malignant disease or eye disorders as glaucoma or a family history of glaucoma.

5. Clinically significant abnormal laboratory values.

6. Unwilling to discontinue use of contact lenses on the day of a treatment visit.

7. Current active eye disease (i.e. any disease for which topical or systemic ophthalmic medication is necessary). In case of historical eye disease, topical or systemic ophthalmic medication should have been stopped for at least one month before the study.

8. Pupillary abnormalities (irregular, very dark iris, iris synechiae, eye movement disorder (e.g. Nystagmus, etc.), dacryocystitis and all other pathologies of tears drainage system

9. Use of any ophthalmic medication except unpreserved artificial tears on the day of a treatment visit.

10. History of inflammatory ocular disease (e.g. iritis, uveitis, herpetic keratitis).

11. History of ocular trauma, infection or inflammation within the last 3 months.

12. Ocular surgery or laser treatment of any kind in the study eye within 3 months.

13. Irregularly-shaped pupil secondary to ocular trauma, intraocular surgery or congenital defect.

14. History of neurogenic pupil disorder (e.g. Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).

15. History of iris surgery of any kind (e.g. iridotomy, iridectomy, coreoplasty).

16. History of previous corneal surgery; iris atrophy, traumatic mydriasis or angle recession, chronic or acute uveitis.

17. Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration and superficial punctuate keratitis).

18. Pseudoexfoliation, exfoliative syndrome.

19. History of closed-angle glaucoma.

20. Subjects with narrow angle prone to glaucoma precipitated by mydriatics

21. Subject undergoing treatment identified as potentially interacting with the IMP, including antidepressant drugs, beta-blockers, other indirect sympathomimetics, alpha sympathomimetics (oral and/or nasal routes), dopaminergic ergot alkaloids, ergot alkaloid vasoconstrictors, selective MAOI-A, linezolid, and halogenated volatile anesthetics.

22. Subject planning to receive an MAOI within 3 weeks following the end of the study.

23. Subjects who have received non-selective monoamine oxidase inhibitors (MAOIs) within the last 15 days

24. History of significant alcohol or drug abuse within one year prior to the screening visit.

25. Regular use of alcohol within six months prior to screening visit (more than 14 alcohol units per week) [1 Unit =150 ml of wine, 360 ml of beer, or 45 ml of 40 % alcohol].

26. Inability to abstain from alcohol for the duration of study period.

27. Positive results for drugs of abuse (barbiturates, marijuana, opioids, benzodiazepines and methadone) in saliva before each administration.

28. Positive alcohol breath test before each administration.

29. Use of soft drugs (such as marijuana) within three months prior to screening or hard drugs such as crack, cocaine or heroin within one year prior to screening visit.

30. Participation in another clinical trial simultaneously.

31. Breastfeeding women.

32. Positive pregnancy test at screening.

33. Females of reproductive age that had sexual intercourse with a non-sterile male partner without highly effective contraception within 14 days prior to drug administration.

6.4 **Restrictions Prior and During the Study**

All subjects will be questioned on the following points/ restrictions prior to treatment administration. If a subject admits non-compliance with the following restrictions, the Principal Investigator or the Co-investigator will decide whether this subject is allowed to remain in the study. Non-compliance with the following restrictions will be recorded.

6.4.1 *Food and Fluids*

No food or water restrictions are applicable prior to administration of the investigational products.

6.4.2 *Alcohol and Drugs*

The subjects must abstain from soft or hard drugs during the study. Moreover, they ought to avoid any alcohol or alcohol-based product consumption from 24 hours prior to drug administration until last ophthalmological examination of each study period.

6.4.3 Prior and Concomitant Therapy

Any pharmacological treatment administered before and during the clinical trial must be registered in the CRF. The investigator, considering the inclusion and exclusion criteria, will decide whether the subject can participate or continue in the clinical trial.

Concomitant medication and dosage, especially of systemic or ophthalmic medications that may affect mydriasis should have been stopped for at least 30 days before entering the clinical trial.

Any new treatment that could interfere with the evaluation of the parameters of the clinical trial is not allowed. It is not allowed the co-administration of new drugs during the study, with the exception of those required for counteracting any adverse events. Contraceptives are allowed. If, against warning, a pharmaceutical product is consumed, the principal investigator/co-investigator will decide whether the subject will be permitted to remain in the study or withdraw. The decision will depend on the kind of drug, the time of intake, etc. The drug and dose will be recorded.

6.4.4 Contraceptive regimen throughout the study

Females with childbearing potential that have sexual intercourse with a non-sterilized male partner will have to take a highly effective birth control to prevent pregnancy during the entire study. Highly effective contraceptive regimens as recommended by the Clinical Trials Coordination Group (CTCG) [20] are described below.

The following are considered as highly effective birth control methods: Established use of oral, intravaginal or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; established use of oral, injected, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine hormone-releasing system or placement of an intrauterine device; bilateral tubal occlusion; vasectomised partner; true abstinence.

7 SUBJECT DISCONTINUATION OF TREATMENT AND DISCONTINUATION OR WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Subject from Treatment

Subject may be discontinued from treatment under the following circumstances:

- Serious Adverse Events: Any subject experiencing a serious or unacceptable adverse event related to the investigational products and/or related to the auxiliary product will be required to discontinue treatment immediately.
- Allergic Reactions: Subjects who exhibit any allergic reactions to the mydriatic agents or any other medications administered during the trial will be withdrawn from treatment.

7.2 Discontinuation of Subject from Trial

All subjects who prematurely terminate participation in the clinical study will be referred to as drop-out.

Subjects will be informed that they keep the right to voluntarily withdraw from the study at any time. The reason for discontinuing from the study should be provided.

Subjects may be terminated from the study due to:

- Non-compliance or significant protocol violation,
- Investigator decision that termination is medically indicated,
- The subject requires treatment with any other medication,
- Voluntary withdrawal from the study,
- Loss to follow-up,
- Other administrative reasons (e.g., study terminated by Sponsor, technical problems, non-compliance with study medication administration or other study requirements, etc.)

7.3 Procedures for collection of data relating to withdrawn subjects

Subjects who terminates due to the occurrence of an AE will be followed until resolution or stabilization of the event.

Any subject who does not come for the scheduled consultation or study assessments or wants to stop the participation in the study should be contacted (by phone) to know if the cause is due to procedures related to the study (e.g. occurrence of adverse event(s)) or if the cause is due to other reasons which are not related to the study (e.g. for personal reasons).

If there is a medical reason for the withdrawal the subject will remain under the supervision of the clinical investigator until pre-study state of health has returned or is at least adequately stabilized.

The investigator has to inform the Project Manager and the Clinical Monitor immediately if a subject must be withdrawn, a subject withdraws from the study treatment and/or withdraws his informed consent. The termination (e.g., date and reason) should be documented in the source records and on the CRF.

Any recorded data of withdrawn subjects will be presented in the final report.

7.4 Replacement of drop-out

In any case, if a subject does not complete the study, the Sponsor decides whether a subject shall be replaced or not. It is planned that a decision on replacement will only be made if more than 2 subjects drop-out from the study.

According to the randomization code replacements of drop-out or withdrawals will be allocated to the same treatment sequence as the subject they replace.

8 TREATMENTS

8.1 Test Product

Denomination:	FDC 08P2002F0 Fixed Dose combination of 0.34 % tropicamide / 2.5 % phenylephrine hydrochloride eye drop solution
Composition:	The active substances in this medicine are tropicamide and phenylephrine hydrochloride The other ingredients are Gellan Gum (Kelcogel CG-LA®), Sodium citrate and water for injection
Pharmaceutical form:	Eye drops, solution
Route of administration:	Ocular use
Dosage:	1 eye drop. Rinsing will be performed with NaCl 30 min after instillation
Duration of treatment:	1 single administration

More information is available in the current Investigator's Brochure of FDC 08P2002F0. FDC 0.34 % tropicamide / 2.5 % phenylephrine hydrochloride is not currently approved in any country.

8.2 Comparative Product

Denomination:	Mydriasert® insert (0.28 mg tropicamide and 5.4 mg phenylephrine hydrochloride)
Composition:	The active substances in this medicine are tropicamide and phenylephrine hydrochloride The other ingredients are Ammonio methacrylate copolymer (Type A), Polyacrylate dispersion 30 %, Glycerol dibehenate, Ethylcellulose.
Pharmaceutical form:	Insert
Route of administration:	Ocular use
Dosage:	1 insert will be kept onto the eye for one hour. Then Insert is retrieved and rinsing will be performed with NaCl after retrieval of insert (performed after a contact time of 60 min).

	Insert will be placed into and removed from the lower conjunctiva fornix of the eye using sterile forceps
Duration of treatment:	1 single administration

More information is available in the current SmPC of Mydriasert® [14]. Mydriasert® has been approved in many countries; the reference used in the study is 34009 353 728 4 0 (1 insert per box) from the French Market. It will be used in the clinical trial in accordance with the conditions described in the SmPC.

All investigational products will be provided by the Sponsor. The batch number(s) will be included in the final study report.

8.3 Auxiliary Product

Denomination:	Saline Solution
Composition:	Sodium chloride (NaCl) 0.9%
Pharmaceutical form:	Eye drops, solution
Route of administration:	Ophthalmic
Dosage:	5 mL
Duration of treatment:	Once 30 min after FDC 08P2002F0 instillation Once 60 min after Mydriasert® administration (i.e. Immediately after Mydriasert retrieval)

[redacted]

8.4 Packaging and labelling

8.4.1 Packaging

The investigational medicinal product 08P2002F0 will be manufactured by the Laboratoire Unither Coutances according to Good Manufacture Practices (GMP) and are suitable for human use.

The comparative product Mydriasert® will be purchased on the Frenck Market.

Labelling for clinical trial, and distributions will be ensured by [redacted]

The IMPs will be released by [redacted] according to written specifications which ensure pharmaceutical quality of the medication.

The primary packaging of IMP 08P2002F0 is a Single dose units (SDU). SDU are packed by 10 in a white Aluminium foil pouch - length of 163 mm and width of 70 mm (secondary packaging).

Then, pouches are placed by 6 in a folding box (tertiary packaging). Consequently, each folding box contains 60 single dose units.

The primary packaging of Mydriasert® is an aluminium pouch containing one ophthalmic insert. Box containing 1 or 20 aluminium pouches (secondary packaging) will be provided. There is no tertiary packaging. Disposable sterile forceps are included in a sachet (transparent PET/PEVA layer and paper layer).

	IMP 08P2002F0	**Comparator**
Primary (I)	1 single dose container	1 aluminium pouch containing 1 ophthalmic insert
Secondary (II)	1 aluminium pouch containing 10 single dose containers	1 box containing 1 or 20 aluminium pouches
Tertiary (III)	1 box containing 6 aluminium pouches	N/A

Table 4: packaging

The Saline solution used in order to rinse the eye after IMP administration for simulating a gesture preoperationally done, will be supplied from EU Market and provided in its original packaging.

8.4.2 Labelling

Container(s) will bear a label containing the name of the drug under investigation, the dosage form, the lot/batch number, the manufacturer, the manufacturing and/or expiry/retest date. The Sponsor is obliged to indicate the storage conditions (e.g. light protection, temperature) of the investigational products and the expiry date.

The content of the labels will be in accordance with the Hellenic regulatory specifications and requirements (i.e. the same as European regulation) and translated into Greek as legally required.

The corresponding label applied on outer packaging of IMPs will contain the following information in Greek:

- The Main contact's name, address and phone number;
- The name of the substance, its strength, its potency;
- The pharmaceutical form, the route of administration and the quantity of dosage units;
- The batch number
- The study code, the clinical site, the investigator and sponsor name;
- The subject number and/or the period number
- The name of the investigator

- The sentence “Refer to protocol for directions for use”.
- The sentence “For clinical trial use only”
- The storage conditions;
- The expiry date in month and year

The final immediate packaging labels of IMP 08P2002F0 will be provided separately to the site by [redacted] at the same time as IMP, and will have to be applied by the pharmacist of the site, the same day of administration, after opening the sachet.

Initial unit dose container for test product will be laserly mark, and will contain IMP code “SLGL”, initial manufacturer batch number and abbreviated Sponsor’s name.

Label for final immediate packaging will contain the following information:

- The Main contact’s name;
- The name of the substance, its strength, its potency;
- The pharmaceutical form, the route of administration
- The batch number
- The study code, the clinical site, the investigator and sponsor name;
- The subject number and/or the period number
- The sentence “Refer to protocol for directions for use”.
- The sentence “For clinical trial use only”

Label for auxiliary product will contain the same required information, translated in Greek.

8.5 **Shipment and IMP reception**

Shipments of IMPs (test product and comparative product) and auxiliary product to site will be organised by the Sponsor's drug distributor (Eurofins-CTS France) at a controlled temperature below 25°C.

Sufficient amount of dosage units to allow BECRO Ltd to conduct the study according to the requirements of the regulatory authorities (European Medicines Agency (EMA) and the Hellenic national organization of medecine (EOF)) will be provided.

Upon receipt, the site will inventory the IMPs and complete the acknowledgement of receipt form which has to be returned to the drug distributor. Should any abnormality of the supply boxes be observed, the site must immediately inform the drug distributor. At delivery by the Sponsor an inventory will be conducted and all pharmaceutical products will be counted (per participant and in total) by authorized personnel. The results will be recorded in the drug accountability/retention record according to BECRO Ltd appropriate SOPs.

8.6 Storage conditions

Principal Investigator or other authorised persons are responsible for storing the investigational medicinal products in a secure and safe place with no access by unauthorized personnel in accordance with local regulations, labelling specifications, policies, and procedures.

Control of investigational products storage conditions (humidity, protection form light; unit dose kept in the sachet until at the latest 7 days before IMP administration, and control of temperature (storage in a controlled temperature under 25°C) should be managed according to the rules provided by the Sponsor.

A temperature log should be maintained and read by site Investigators or other authorised persons on a daily basis in the room of investigational products storage. This log can be replaced by the printing of a daily temperature curve if site is using a calibrated electronic thermometer. Thermometers should be regularly calibrated.

8.7 Method of Assigning Subjects to Treatment Groups

The test product or the comparative products will be assigned at T0 according to the randomization method presented in Section 5.2.

8.8 Method of administration

8.8.1 Test product

Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product.

IMP 08P2002F0 should be applied into the conjunctival sac after eyelid retraction, while the subject is in a supine position. After application, the treated eye should be closed for 1-5 minutes while the lacrimal sac is compressed appropriately.

30 min after IMP administration, eye should be rinsed with saline solution provided (auxiliary product). 5 mL should be applied.

8.8.2 Comparative product

Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product.

Mydriasert® should be applied as described in the SmPC [14] :

- Cut the sealed edge along the dotted line, open the sachet and locate the insert.

- Hold the insert with disposable sterile forceps with rounded ends provided in the packaging, making sure not to damage it.
- Pull down the lower eyelid by pinching it between the thumb and index finger, and apply the ophthalmic insert, using the disposable sterile forceps, in the lower conjunctival sac.

60 min after IMP administration, insert should be removed from the lower conjunctival sac as described in the SmPC, i.e. by using either sterile surgical forceps, or a sterile swab or a sterile irrigation or washing solution, by lowering the lower eyelid.

In any case, eye should be rinsed with saline solution provided (auxiliary product). 5 mL should be applied.

8.9 Product return and compliance

A record of IMPs and auxiliary product dispensed and taken will be reported in the CRF.

At the end of the study, there will be a final reconciliation of product shipped, product consumed, product remaining and treatment disposed. This reconciliation will be recorded in the site study drug log, signed and dated.

IMPs will either be disposed at the study site according to the study site's institutional standard operating procedure or be returned to [redacted] with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Any discrepancies noted will be investigated, resolved and documented prior to destruction.

Accurate records of IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on appropriate form.

8.10 Recall

If an IMP batch is suspected to be defective, the Investigator and/or the Pharmacist will be immediately informed by the Sponsor or its representative.

IMP must immediately be put in quarantine and no further administration of the concerned batch(es) must be done until Sponsor's written instructions.

9 STUDY PROCEDURES

Unless otherwise specified in this protocol, all procedures related to the study quality will be conducted according to the Standard Operating Procedures (SOPs) of BECRO. A plan of the study schedule and the planned examinations at every visit of this study is presented in Appendix SCHEDULE OF ASSESSMENT

Table 1: study flowchart

and will be explained in the following paragraphs.

9.1 Description of Study Days

9.1.1 Subject Evaluation prior to Study Initiation

Potential study volunteers will be examined prior to study initiation in order to determine their eligibility for participation. The following examinations will be performed within 15 days prior to administration of study medication:

9.1.1.1 Medical History

Medical history will include evaluation of the eyes, ears, nose, throat and any cardiac, vascular, pulmonary, musculoskeletal, gastrointestinal, neurological, endocrine, psychiatric, dermatological, hematologic and allergic disorder or disease.

This examination will include questions with the purpose of establishing the medical history of the volunteers.

9.1.1.2 Physical Examination

The physical examination will include demographic data (height, weight, body mass index (BMI), age, gender and smoking habits), vital signs (blood pressure, pulse rate, and body temperature), evaluation of the eyes, ears, nose, throat, peripheral vasculature, lungs, musculoskeletal system, abdomen, neurological function, endocrine system, skin and immunology.

9.1.1.3 Ophthalmological examination during screening

The Investigators will assess the eyes by slip lamp examination. Any finding that is not within the normal range of clinical acceptability will be assessed by the Principal Investigator for its clinical significance. All values will be reported in the Case Report Form (CRF).

- Slit lamp examination

The slit lamp examination uses an instrument that provides a magnified, three-dimensional (3-D) view of the different parts of the eye. During the examination all tissues of the eye and some of its adnexa are revealed. It is routinely used for the examination of the anterior segment of the eye, which includes the anterior vitreous and those structures that are anterior to it. (cornea, iris, anterior chamber, crystalline lens). The eyelids, other adnexa and the conjunctiva are examined.

By special lenses between the slit lamp and the cornea (or directly on the cornea) deeper structures of the eye are investigated, such as the posterior vitreous, the optic nerve head, the retina, and the area where aqueous humour drains out of the eye (drainage angle/angle of the posterior chamber). A camera may be attached to the slit lamp to take photographs of different parts of the eye. Fluorescein dye eye drops may be used during a slit lamp examination to make it easier to detect a foreign body, a tear film abnormality or an infected or injured area on the cornea.

Ocular findings on slit-lamp bio-microscopy are graded on a scale of 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe.

9.1.1.4 Other Examinations

An electrocardiogram (ECG) will be performed.

9.1.2 *Study Days*

9.1.2.1 Tests at Check-in

Eligible subjects will arrive at the clinic, at least 1 hour prior to study drug administration. Pregnancy testing in urine will be conducted in female volunteers at reproductive age. All subjects will be examined by the medical investigators for general well-being within one hour pre-IMP administration. Once vital signs (i.e. blood pressure, pulse rate and body temperature) will be measured, then, ophthalmological examination will be performed. The examination will include pupil diameter photography.

9.1.2.2 Administration of IMPs

The treatments will be administered by one of the Investigators. This investigator is the not-masked investigator, whereas the Investigator that will perform the study assessments will remain masked for the remain of the study (masked Investigator).
The treatments will be administered as described in section 8.8
The two periods will be separated by a washout period of ≥ 2 days up to ≤ 7 days.

9.1.2.3 Health Status Monitoring

Subjects will be under the surveillance of the medical investigators for six hours following each drug administration. The investigators will remain available at any time during the entire study period. In case of serious adverse events, the subjects will remain in the clinic as much as required after ophthalmological examination termination according to the judgment of the Principal Investigator. The aforementioned procedures will be applied for each period.

9.1.2.4 Study Termination

The study will be terminated once the last phone call of the last volunteer is performed.
The medical investigator will evaluate each abnormal value to determine if it is clinically significant. Clinically significant laboratory values will be reported as adverse events (AE). All laboratory values will be reported in the CRF.

9.2 **Ophthalmological assessment during study periods**

9.2.1 *Pupil diameter measurement*

The pupil diameter will be measured by the masked Investigator.

In each period, pupil diameter of each subject will be recorded by the not-masked Investigator.

The measurements will be performed according to the following scheme: one measurement will be performed prior to drug administration (within one hour pre-dosing), and thereafter at 10 min (± 2 min), 20 min (± 2 min), 30 min (± 2 min), 45 min (± 5 min), 60 min (± 5 min), 1 h 15 (± 5 min), 1 h 30 (± 10 min), 2 h (± 10 min), 2 h 30 (± 10 min), 3 h (± 10 min), 3 h 30 (± 10 min), 4 h (+/- 10 min), 4 h 30 (± 10 min), 5 h (± 10 min), 6 h (± 10 min) post-administration. The complete schedule of measurement times is presented in **Table *2***.

The actual measuring time will be calculated according to the drug administration schedule. The actual measuring time will be used for the statistical analysis. The actual clock time of every measurement will be recorded and reported in the subject's CRF.

Any deviations from the scheduled measurement time greater than two minutes (> 2 min) for the measurements up to 30 min (included), greater than five minutes for the measurements from 45 min to 1h 15 (included), and greater than ten minutes (> 10 min) for the measurements after 1 h15 hours will be reported in the final study report.

9.2.2 Subject Discomfort

Discomfort questionnaire will be answered by subject at 10 min (± 2 min), 30 min (± 2 min), 60 min (± 5 min), 2 h (± 10 min), and 6 h (± 10 min) post-administration.

Healthy volunteers will be asked to respond regarding the following ocular signs after instillation of the respective IMP: irritation/burning/stinging, eye dryness, foreign body sensation, blurred vision by "yes" or "no" and to assess the severity by grading 0 = none, 1 = slight, 2 = moderate, 3 = severe, if sign(s) were noted with "yes".

9.3 Safety Monitoring

Subjects will be monitored during the entire study period for AEs. Each subject will be provided with a card containing the study code, the administered medication and the contact details of the investigator. In each period the Principal Investigator/co-investigator will be responsible for drug administration and will remain at the clinical site for the first six hours following each drug administration. Should the subjects visit their doctor or dentist, they will be advised to notify the latter of their participation in a research study on a fixed dose combination of tropicamide 0.34 % and phenylephrine hydrochloride 2.5 % eye drop Solution before taking any medicines or undergoing any medical procedure.

9.3.1 Vital Signs

In each period vital signs (blood pressure, pulse rate and body temperature) will be measured and recorded prior to each study drug administration. Vital signs will also be evaluated at 3 and 6 hours (± 20 minutes) post-administration. Further measurements will be performed if judged necessary

by the investigator. Blood pressure and pulse rate measurements will be performed in seated position.

9.4 Data Collection and Evaluation

All clinical data will be recorded by the clinical staff on clinical chart and transferred to the CRFs. The investigators will be responsible for complete and accurate clinical data recording according to the SOPs of BECRO.

10 SAFETY ASSESSMENT

10.1 Reference Safety Information Document

The current version of the Investigator Brochure of FDC 08P2002F0, will be the Reference Safety Information document to assess the expectedness of AEs. Section 6 (table 9) of the IB will be used for assessing the expectedness for FDC 08P2002F0.

Section 4.8 (Adverse Effects) of the SmPC will be used for assessing the expectedness for Mydriasert®.

FDC 08P2002F0 is currently in clinical development for the indication of mydriasis. Identified and potential risks associated with IMP will be closely monitored throughout the clinical study.

First administration of IMP will be performed in a hospital, clinic environment under close supervision of the investigator or a medically qualified staff member. All adverse events and serious adverse events will be recorded during the study until 3 days (+/- 1) after the last IMP administration.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

10.2 Benefit / Risk Information

10.2.1 Potential risks related to the IMPs

FDC 08P2002F0 is an IMP which is the combination of two active ingredients. As a result, subjects treated with FDC 08P2002F0 might experience the adverse reactions already reported in the SmPCs for tropicamide and phenylephrine hydrochloride ophthalmic administration.

Contraindications

Contraindications do not differ from those of Mydriasert®.

FDC 08P2002F0 is contraindicated in patients with a known hypersensitivity to tropicamide and/or phenylephrine hydrochloride or any of the other constituents.

Mydriasert® is contraindicated in patients with angle-closure glaucoma: patients with angle-closure glaucoma (not previously treated by iridectomy) and patients with a narrow angle, predisposed to glaucoma triggered by mydriatics. Same contra-indication is expected with FDC 08P2002F0. To minimize risk, subjects with a history of angle-closure glaucoma as well as subjects with a narrow angle, predisposed to glaucoma will be excluded for the clinical study.

Some combinations with other products are contra-indicated as described in section "interaction" below.

Special warnings and special precautions for use

Special warnings and precautions for use do not differ from those of the tropicamide and phenylephrine hydrochloride indicated in their SmPCs.

Potential risks are related to phenylephrine:

- As with all eye drops, phenylephrine can pass into the general circulation.

In order to avoid systemic effects induced by the passage of phenylephrine into the general circulation via the nasolacrimal tracts, the skin and oral ingestion, the following actions should be taken:

- Wipe off excess eye drops that flow onto the cheek to avoid any risk of ingestion
- Close the eye and at the same time compress the inner corner of the eye for 1 minute after instillation in order to occlude the lacrimal points. The risk of toxicity is higher in the elderly.

Phenylephrine eye drops should be administered with caution to patients at risk, particularly cardiovascular risks: hypertension, coronary insufficiency, hyperthyroidism, rhythm disorders. Such subjects will be excluded for phase I/II study.

Ocular hyperaemia can increase the absorption of phenylephrine given topically.

Potential risks will also be related to tropicamide:

- With eye drops, there is a passage of tropicamide into the general circulation.
- The risk of toxicity is higher in the elderly.
- In order to avoid systemic effects induced by the passage of tropicamide into the general circulation via the lacrimal tract and by oral ingestion, it is recommended, especially in the elderly, to compress the internal angle of the eye for 1 minute after each instillation and to wipe the excess on the cheek.

- Tropicamide may trigger an acute glaucoma attack by mechanical obstruction of the aqueous humor elimination pathways in subjects with a narrow iridocorneal angle.
- Open-angle glaucoma: Tropicamide eye drops may be used in chronic glaucoma after checking that the angle is open.
- Tropicamide eye drops should be administered with caution to patients with symptoms of central nervous system disease, as this drug may cause central nervous system disorders.
- Tropicamide eye drops should be used with caution in cases of prostatic adenoma.
- Avoid contact with soft contact lenses. Remove contact lenses before application and wait at least 15 minutes before reinserting them.

In order to minimize risk, subjects with such concomitant disease will be excluded from clinical studies.

Interactions

No formal drug interaction studies have been performed with FDC 08P2002F0, but interactions are expected to do not differ from those of other similar products.

Mydriasert® (combination tropicamide 0.28 mg and phenylephrine HCl 5.4 mg) does not mention any study regarding interactions.

Mydrin-P® (combination tropicamide 0.5 % and phenylephrine HCl 0.5 %) indicates precautions on concomitant use as followed:

Name of agent	Clinical symptoms, and treatment	Mechanism and risk factors
MAO inhibiters (during treatment and within 3 weeks after treatment)	A rapid increase in the blood pressure may occur	MAO inhibiters may inhibit metabolic enzymes of this drug, and may increase catecholamine sensitivity.
Tricyclic or tetracyclic anti-depressants: maprotiline hydrochloride, clomipramine hydrochloride, amoxapine	A rapid increase in the blood pressure may occur	These drugs may inhibit norepinephrine reuptake at sympathetic nerve endings, and may increase the concentration of epinephrine at receptor sites.

Visumidriatic fenilefrina® (combination tropicamide 0.5 % and phenylephrine HCl 10 %) advises to use with great caution in patients undergoing treatment with antidepressant drugs and beta-blockers.

Mydriaticum® (tropicamide 0.5 %) specifies that although administered locally, it may cause systemic effects that should be taken into account.

Neosynephrine 2.5 % Faure® (phenylephrine HCl 2.5 %) specifies that although administered locally, this drug may cause systemic effects that should be taken into account.

- Contraindicated combinations
  - Non-selective Monoamine oxidase inhibitors (MAOIs)

Paroxysmal hypertension, hyperthermia that can be fatal. Due to the duration of action of the MAOI, this interaction is still possible 15 days after stopping the MAOI.

- Other indirect sympathomimetics
  Risk of vasoconstriction and/or hypertensive crises.
- Alpha sympathomimetics (oral and/or nasal routes)
  Risk of vasoconstriction and/or hypertensive surges.

- Not recommended combinations
  - Dopaminergic rye ergot alkaloids
    Risk of vasoconstriction and/or hypertensive surges
  - Ergot alkaloids vasoconstrictors
    Risk of vasoconstriction and/or hypertensive surges.
  - Selective MAOI-A
    Risk of vasoconstriction and/or hypertensive surges.
  - Linezolid
    Risk of vasoconstriction and/or hypertensive surges.
- Associations requiring precautions for use
  - Halogenated volatile anesthetics
  - Intraoperative hypertensive surge.
    It is important that the anesthesiologist be informed of the administration of phenylephrine eye drops before or during the ophthalmic procedure.
- Associations to be taken into account

  Not applicable

Adverse reactions with FDC 08P2002F0

Adverse reactions expected do not differ from those from tropicamide and phenylephrine contained in Mydriasert® (0.28 mg/5.4 mg ophthalmic insert).

Table 6 below is presented according to the MedDRA system organ classification (SOC) and Preferred Term Level.

The expected frequency of adverse reactions is presented in the table 6 below in CIOMS frequency categories:

- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);

- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Undesirable effects based on undesirable effects reported with Mydriasert® (0.28 mg/5.4 mg ophthalmic insert),

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to <1/10	Uncommon ≥ 1/1,000 to <1/100	Rare ≥ 1/10,000 to <1/1,000	Very Rare <1/10,000
Nervous system disorders					Convulsions
Eye disorders		Stinging; Blurred vision; Visual discomfort.	Tearing; Irritation; Disabling mydriasis because of prolonged pupil dilation; Photophobia; Superficial punctuate keratitis.	Blepharitis; Conjunctivitis; Risk of angle-closure glaucoma; Intraocular hypertension.	

Very rare cases of corneal ulcer and corneal oedema were observed due to forgotten insert.

Although administered via the topical route, the mydriatic agents contained in this insert may cause the following systemic effects which must be taken into account:

- elevation of blood pressure, tachycardia,
- very rarely, major accidents such as cardiac arrhythmia,
- tremor, pallor, headaches, dry mouth.

Paediatric population

- Eye disorders:

Periorbital pallor in preterm patients – Frequency not known (cannot be estimated from the available data).

- Respiratory, thoracic and mediastinal disorders:

Pulmonary oedema – Frequency not known (cannot be estimated from the available data).
Reporting of suspected adverse reactions

Effects on ability to drive and use machine

Subjects who receive a mydriatic may suffer from photophobia, stinging and temporarily blurred vision and this may impair their ability to drive under certain circumstances. Warn subjects not to drive or operate hazardous machinery until vision is clear.

10.2.2 Potential risks related to the Auxiliary product: Sodium Chloride 0.9 %

No Contra-indication, undesirable effect or risk is indicated in the Instruction for Use of Sodium Chloride

10.2.3 Benefit/Risk Balance

FDC 08P2002F0 is not currently approved in any country.

However, tropicamide and phenylephrine hydrochloride are worldwide registered and marketed since a wide, both alone or in combination.

New drug developments let society benefit from pharmaceutical alternative with more relevant solutions.

The risk a healthy subject would encounter from taking two administrations of tropicamide/phenylephrine hydrochloride from Test Product and Reference Product, with at least 2-days washout interval is small. If adverse events occur from the study drug or study procedures, they are expected to be mild and minimal and within the commonly reported ones.

For all these reasons, it is judged that participation in the study does not induce significant risk for subjects.

10.3 Definitions in relation with the vigilance

10.3.1 Adverse Event (AE)

Any untoward medical occurrence in a subject or a clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

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

Adverse events fall into the categories ‘’non serious’’ and ‘’serious’’

10.3.2 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).

The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All unfavorable events judged by the investigator or the Sponsor to have a causal relationship with an investigational product are characterized as ADR.

10.3.3 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

10.3.4 Serious Adverse Event

A serious adverse event (SAE) is classified as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires subject hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect.

10.4 **Collection, assessment and reporting of AE, ADR and SAE**

10.4.1 Procedures for Collection and Reporting of Adverse Events (AEs)

After signing the informed consent, any adverse Events (AEs) (including clinically relevant laboratory values and vital signs) serious or not, will be monitored over the entire course of the study and if possible until its resolution. Prior to drug administration of the second period the subjects will be questioned on having experienced unusual symptoms that may have occurred since the previous administration of the study drug(s). Subjects will inform study personnel for every adverse event that might occur throughout the study. All symptoms will be recorded and evaluated prior to next administration if necessary, lab tests will be performed in order to confirm the resolution of the AE.

The AEs, either spontaneously reported by a subject or mentioned upon open questioning by a member of the investigator team personnel or observed by the investigators will be documented at first in a source document. Subsequently, all relevant information will be transferred to the CRF and assessed by the investigators.

Recording of Adverse Events

The adverse events (AE) will be recorded and evaluated for their seriousness, severity, and relationship to the study medication. During the course of the study, the AE will be collected and documented. For the purposes of this study, the period of AE observation for each subject will extend until 3 days (+/-1) after the last study drug administration. The AE will be followed-up until complete resolution or until the investigator judges safe to discontinue follow-up. The observation results will be forwarded to the Sponsor. The AEs will be coded using the adverse event dictionary MedDRA.

10.4.2 Assessment of Adverse Events

The investigator should evaluate the following parameters for any adverse event recorded within the research:

- Intensity,
- Causality,
- Severity,
- Unexpectedness.

Assessment of Intensity

The assessment of the intensity accords with Common Terminology Criteria for Adverse Events (CTCAE) V5.0:

Mild adverse event:
- asymptomatic or mild symptoms,
- clinical or diagnostic observations only,
- intervention not indicated.

Moderate adverse event:
- minimal, local or non-invasive intervention indicated,
- limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Severe adverse event:
- medically significant but not immediately life-threatening,
- hospitalization or prolongation of hospitalization indicated,
- disabling,

- limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Causality assessment

In the CRF, the causality link is evaluated:
- Compared to research (act, method, related products…),
- Compared to study products (active/comparative),
- According to the criteria: excluded, not excluded.

The causality could be considered as ‘’excluded’’, only whether:
- A clear alternative explanation exists, AND/OR,
- The event occurs according to a chronology incompatible with the time of study product intake and/or with the study conduct, AND/OR,
- The relationship between research and the event is not plausible.

The causality could be considered as “not excluded”, only whether:
- The event occurs according to a chronology compatible with the time of study product intake and/or with study conduct AND/OR,
- The relation between the event and the research is plausible, but the event could also be explained by a concurrent disease or other drugs or chemicals OR,
- The event is part of adverse events expected in the context of the research.

In the SAE notification report, the causality link will be also evaluated:
- Compared to the research (without link with study products),
- Compared to study products,
- Compared to other factors to be specified,
- According to the criteria: not related, possibly, likely, certain.

The causality could be considered as “certain’’, only whether the event occurs according to a chronology compatible with the time of study product intake and/or with study conduct AND:
- The event is part of adverse events expected in the context of the research OR,
- The relation between the event and the research is plausible and could not be explained by a concurrent disease or other drugs or chemicals AND whether ‘’dechallenge’’ and ‘’rechallenge’’ are positives (if applicable).

The causality could be considered as ‘’Likely’’ only whether the event occurs according to a chronology compatible with the time of study product intake and/or with study conduct AND:
- The event is part of adverse events expected in the context of the research OR,
- The relation between the event and the research is plausible and could not be explained by a concurrent disease or other drugs or chemicals AND whether ‘’dechallenge’’ is positive and ‘’rechallenge’’ is not available or inconclusive (if applicable).

The causality could be considered as "Possible'' only whether the event occurs according to a chronology compatible with the time of study product intake and/or with study conduct AND /OR:

- The event is part of adverse events expected in the context of the research OR,
- The relation between the event and the research is plausible and could not be explained by a concurrent disease or other drugs or chemicals AND whether ''dechallenge'' is not available or inconclusive (if applicable).

The causality could be considered as "**Not related**'' only whether:

- A clear alternative explanation exists, AND/OR,
- The event occurs according to a chronology incompatible with the time of study product intake and/or with the study conduct, AND/OR,
- The relationship between research and the event is not plausible.

Assessment of the unexpected nature

The assessment of unexpected nature of the adverse event is based on the information described in the protocol or in the technical file relating in particular, where appropriate, to acts and methods carried out during the research or products being used for the research or for the purpose of the research.

If an adverse effect concerns a health product used for the trial purposes, it is appropriate to determine the unexpected nature of this effect, to refer to the information contained in repositories in force if the product is used in accordance with these.

10.5 Notification of serious adverse event and reaction, or SUSAR

The Principal Investigator/Co-Investigator shall report any Serious Adverse Event (SAE) to Pharmacovigilance CRO (Product Life Group) by sending SAE forms (see appendix 17.2) without undue delay but not later than within 24 hours of obtaining knowledge of the events, whether deemed drug-related or not (see contact details hereafter) during the trial duration (i.e until last phone call planned 3 days (+/-1) after the last IMP administration.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious event to the Sponsor.

The notification must be done without delay from the time(s) he/she is aware of the event.

This procedure should be written (via e-fax or e-mail). As soon as feasible, a report will be submitted by the Investigator to the Sponsor representative (Product Life Group) including full documentation of the course of the SAE, any therapy given, relevant findings/records, relevant follow-up information and the outcome of the SAE, as well as a causal relationship of the SAE to the Investigational Products.

The original copy of the Serious Adverse Event Form and the fax confirmation sheet should be kept with the CRFs at the study site.

Table 4: SAE Timeframe

"Initial" SAE form	**"Follow-up" SAE** form
IMMEDIATELY **and no later than 24 hours** as of awareness of the SAE	**IMMEDIATELY** **and no later than 24 hours** as of availability of essential follow-up information

Transmission

In the case of a SAE, the investigator must Complete the relevant CRF pages and a pharmacovigilance form with all available initial information.

The SAE reports (pharmacovigilance form) should be e-mailed or faxed [redacted]

The investigator must also record the SAEs, SARs and Suspect Unexpected Serious Adverse Reaction (SUSARs) in the form ''adverse event'' of the CRF.

If all the information is not available at the time of the initial SAE notification to the Sponsor, the investigator must complete the report as soon as possible with the complementary information (within 5 days after initial notification).

Information concerning the follow-up of serious adverse event should be reported by the investigator within the same deadline.

If a non-serious adverse event becomes serious, this one and any relevant follow-up information should be transmitted to the Sponsor or authorized personnel immediately, as described above.

Any suspicion of serious adverse effect already reported to the authority must be reported again in case of accentuation.

The Investigator will notify the Administrative Board of the Hospital of any Suspect Unexpected Serious Adverse Reaction, (SUSAR) resulting in death or being life-threatening (within 7 days) as well as of any other SUSAR (within 15 days).

The Sponsor representative for pharmacovigilance (Product Life Group) will evaluate the causal relationship of the AE as well as their unexpected nature and in the case of SUSARs he / she will notify the Eudravigilance database:

- in case of fatal or life-threatening suspected unexpected serious adverse reactions the notification should be performed as soon as possible, and in any event not later than 7

calendar days after the sponsor became aware of the reaction, followed by a complete report within 8 additional calendar days in case the initial report was incompleted;
- for all other serious, unexpected ADRs notification should be as soon as possible but no later than 15 calendar days after the sponsor became aware of the reaction.

The sponsor has to disclose to the relevant hospital committees, and Eudravigilance database any information related to the safety of the investigational medicinal products.

10.6 **Follow-up of adverse event and reaction**

The investigator will need to follow the subject until the end of his/her participation in the trial.

At the end of the participation of the subject:

- If an adverse event unrelated to the research or study products of the research is in progress, the investigator must guide the subject to his/her general practitioner, if applicable.
- If a serious adverse event is in progress, the investigator must report any evolution of the event to the Sponsor.
- If a suspicion of AR or SAR is in progress at the end of the participation of the subject, the investigator must organize his/her follow-up together with the subject's general practitioner (if applicable). This follow-up will permit to document the evolution of the event until it will be decided to close it (in case of resolution or stabilization) or until causality can be excluded.
- The Sponsor has to declare, in a follow-up report to Eudravigilance, additional relevant information concerning the unexpected SAR and SUSAR:
    - For SUSAR having caused death or life-threatening, this information will be notified within the 8 days from the declaration.
    - For other SUSAR, additional relevant information has to be notified within an additional 8 days from the declaration.

10.7 **Pregnancy**

Pregnancy in a study subject must be reported to Pharmacovigilance CRO (Product Life group) within 1 working day of the site becoming aware of the pregnancy. Subject s who become pregnant during the study must be discontinued from IMP (see section 12.11)

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to Pharmacovigilance CRO (Product Life Group) immediately after the site becoming aware of the event.

10.8 **Emergency Medical Contacts**

To ensure the safety of study subjects, for urgent medical matters or questions, the Investigator may contact: [redacted] be available 24 hours per day, 7 days per week.

11 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis. Just before the database is locked, all problematic cases where evaluability remains unclear will be scrutinized by the responsible data manager, the biostatistician assigned to the study, and the study manager.

11.1 **Sample size**

No prospective calculations of statistical power are made as this study is being conducted as a preliminary study.

A total of 20 healthy volunteers (i.e. 10 subjects in each sequence) of both genders will be included in the study and treated with the investigational products.

11.2 **Statistical Analysis**

Demographic parameters as well as safety data will be summarized descriptively.

The primary endpoint (change in pupil diameter at 60 min from the time of first dose versus baseline) is analyzed using a general linear model for a cross-over design.

The secondary endpoints (corresponding to secondary efficacy objectives) will be analyzed with general linear models, or paired t-test, for continues variables and chi-squared test for categorical variables.

A result is considered significant at $p< 0.05$.

The statistical analysis will be done in full agreement with the International Council for Harmonization (ICH) Topic E9, Statistical Principles for Clinical Trials. Detailed description of analyses will be provided in Statistical Analysis Plan approved before Database (DB) lock.

Safety data will be listed by individual subject and summarized using descriptive statistics.

All AEs, Serious Adverse Event (SAE), non-serious AEs-related to IMP, or AE leading to interruption and discontinuation of IMP will be described.

Number of events, number and percentage of subjects with at least one event and incidence rate, AEs intensity and severity will be also reported.

11.3 Subject Population Analysis

Safety population: The safety population comprises all subjects who have received at least one application of the Test or Reference.

ITT population: The intent-to-treat (ITT) population includes all randomized subjects who had at least one post baseline assessment.

PP population: The per-protocol (PP) population includes all subjects of the ITT population without major protocol violations, who were compliant subjects, and did not withdraw from the study.

12 ETHICS, REGULATORY CONSIDERATIONS AND QUALITY ASSURANCE

The study will be conducted in accordance with the requirements of the European clinical trial Regulation No 536/2014, relevant guidelines [21,22, 23], and ethical principles that have their origin in the Declaration of Helsinki as well as regulatory requirements of the National Organization for Medicines (EOF). The trial will only start when Hellenic Ethics Committee approval and the National Organization for Medicines authorizations are obtained.

12.1 Approval/Favorable Opinion of National (Hellenic) Ethics Committee and National Organization for Medicines (EOF)

Investigators are obliged to submit to the National Ethics Committee (NEC) and EOF all appropriate documents, as well as a copy of the protocol and amendments (if any), the Informed Consent Form (ICF) and the Investigator's Brochure (if required) or Summary of Product Characteristics for approved products, any advertisement for volunteers' recruitment or any other written information that the study subjects will be given.

12.2 Informed Consent Form (ICF)

Prior to a subject's inclusion in the study, the subject will be given a full explanation of the study objective, the study procedures and the potential hazards. The subject should have enough time and opportunity to inquire about study details. All his/her questions should be answered in a satisfactory manner. Once this information is provided and fully understood, the subject is invited to read, sign and personally date the original ICF prior to his/her enrollment and any study procedure.

The ICF should be also signed and dated by the medical investigator/co-investigator who conducted the informed consent discussion. Subjects will be provided with a copy of their signed and dated ICF as well as with a statement that they keep the right to withdraw at any time without giving reasons.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study, specify the version of ICF and the date the written consent was obtained.

If the ICF is subjected to amendments, a new consent of the subjects should be given. The amended ICF should have been approved by the NEC before signed by the subjects.

12.3 **Case Report Form (CRF)**

BECRO Ltd will provide the CRF to be completed, signed and dated by the medical investigator/co-investigator. A sample of the CRF will be submitted with the final integrated study report.

The investigator will document subject data in his/her own files. These subject files will serve as source data for the study. All CRF data required by this protocol will be recorded by investigative site personnel. All data entered into the CRF will be supported by source documentation of the site.

The Principal Investigator is responsible for the accuracy, completeness and legibility of the data reported to the Sponsor in the CRFs and in all required reports. Each CRF must be signed or initialed by the Principal Investigator, signifying agreement with and responsibility for the recorded data. Any corrections to a CRF should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the Principal Investigator's review and signature of the completed CRF have to be resigned and dated with an actual date by the Principal Investigator.

The Principal Investigator should maintain a list of the individuals authorised to enter data into the CRF and to make data changes.

The CRFs will be checked for completeness and plausibility.

12.4 **Data Safety monitoring board**

No Data Safety Monitoring Board (DSMB) will be set-up for this study for the following reasons:

- Tropicamide and Phenylephrine HCl are used in current medical practice as mydriatics with a favourable benefice/risk ratio.
- Dosages administered in this study are not superior to current practice.
- Neither interim analysis, nor arbitration on study continuation or early termination or redesign is planned

12.5 **Compliance**

This study will be conducted in compliance with the Protocol, the Good Clinical Practice (GCP) guidelines, and ethical principles that have their origin in the recent version of the Declaration of Helsinki as well as the requirements of the Ministerial Decree ΔΥΓ3α/79602 (Modification of the common ministerial decree ΔΥΓ3α/89292/31-12-2003 on the harmonization of the Greek legislation to the corresponding Community one in compliance with Regulation No

536/2014ΔΥΓ3(α)/οικ.18910/2013 and Γ5α/59676/22-12-2016. Moreover, the study will be conducted in adherence to the following regulatory requirements of EOF:

- *Decision EOF* 12296/22-3-2001
- *Circular-Decisions of CA (EOF)* 10301/11-2-2010 and 88148/23-12-10.

12.6 **Insurance**

The Sponsor certifies subcontracting a contract of public liability insurance covering possible damage or injuries that could be caused to subjects as a result of the clinical trial.

This policy will cover the responsibilities of the sponsor, the investigator and collaborators, and the head of the site where the clinical trial is being conducted. The insurance policy must cover all subjects throughout the study from initiation to termination.

According to Greek legislation, the Sponsor is liable for any direct or indirect damage caused to the participant by the administration of the drug or any clinical intervention or procedure during the study participation, which would not have taken place if the participant has not taken part in the study. All serious adverse events are covered and secured, in accordance with the Ministerial Decision DYG3 / 89292 / 31.12.2003. Specifically, the insurance covers all subjects throughout the study from the start until the end of study.

The Sponsor is exempted from that liability if the damage is due solely to the fault of the participant or failure to observe the instructions given.

In case of injury or disability resulting from participation in the study, the subject is requested to promptly inform the Investigator responsible for the study.

In case a pregnancy occurs and the neonate experiences health problems due certainly to the investigational medicinal product, even though the protocol and informed consent form provided specific detailed information on the risks of the IMP and to prevent pregnancy and although the study subject received all appropriate contraceptive measures, then these subjects are also covered and secured by the Insurance Policy.

The Insurance certificates will be provided to the Ethics Committee and national Competent Authority at the submission for clinical trial approvals.

12.7 **Investigator Commitments and Duties**

The Principal Investigator should ensure that all persons assisting the study are adequately qualified, informed about the protocol, any amendments to the protocol, the investigational products as well

as their duties and study procedures. The investigator should assign the co-investigators and other qualified persons their duties in the study in written and fill in the Delegation form.

12.8 **Monitoring**

The study will be supervised by a Clinical Monitor. The Principal Investigator will be contacted by the Clinical Monitor on a regular basis.

At this opportunity, the progress of the study will be discussed with the Principal Investigator and the CRFs will be checked for completeness and consistency. The informed consent forms will also be checked by the Clinical Monitor.

Given adequate supervision and guarantee of confidentiality, the Principal Investigator will allow the Clinical Monitor to cross-check the data entered in the CRFs with the source data at the study site and to observe the study procedures in order to verify adherence to the Clinical Study Protocol and to the principles of Good Clinical Practice.

During this study monitoring visits (initiation visit, routine visit(s) and close-out visit) will be performed.

Further details of monitoring and monitoring visits will be described in a Monitoring Plan in accordance to the Note for Guidance on Good Clinical Practice, ICH E6 (R2)[23].

The monitoring report will be submitted to the Project Manager of BECRO Ltd and afterwards forwarded to the Sponsor.

12.9 **Quality Assurance (QA)**

All stages of the clinical, bioanalytical and statistical part of the study together with all related documents will be evaluated by BECRO Quality Manager to ensure that the study is conducted in accordance with the Good Clinical Practice [23], the SOPs and the applicable regulatory provisions of the EOF. The final report will be verified to ascertain that the described methods and reported results are consistent with the primary results obtained during the study.

12.10 **On-Site Audits/Inspections**

According to the Good Clinical Practice, inspections by health authority representatives - including foreign authorities – and Independent Ethics Committees are possible at any time.
In addition, representatives of the sponsor may visit the clinical research facility and CRO in charge, at any time, in order to maintain current and personal knowledge of the study, audit the original study documents and discuss with the investigators on the study progression. The investigator will be informed about the outcome of the audit.
Auditing will be performed by the independent QA personnel of BECRO Ltd in accordance with the requirements of Note for Guidance on Good Clinical Practice [23] in order to systematically

checks the compliance of the study process, reliability and credibility of data and will be performed at every step of the clinical study process and applied to each stage of data handling

12.11 Early Termination or Study Discontinuation

The study is likely to be terminated by the Principal Investigator following Sponsor notification, by the Sponsor or by the Regulatory Authorities. In case of early termination, the Sponsor should notify EOF and NEC without any delay and within 15 days after the study termination, accurately explaining the reasons and describing measurements of subject surveillance, if any, that are to be taken for safety reasons. The Sponsor should also immediately notify the investigators that the required procedure for the Regulatory Authorities notification has been undertaken.

12.12 Study Termination

For safety reasons the end of the study is defined as 3 days (+/- 1) after the last IMP administration of the last subject of the second period. The Sponsor within 15 days since study termination should notify through Clinical Trials Information System (CTIS) that the study has terminated.

13 FINAL REPORT

Following study termination BECRO should prepare an integrated final study report according guidance on structure of clinical study report [25], which will include clinical, and statistical parts [24] and will be signed at least by the Principal Investigator and the Coordinating Investigator. In case of early termination or study discontinuation, BECRO Ltd should produce a summary report on safety.

The final report will be stored in the Sponsor's archive. The summary report is part of the end of trial notification, albeit usually submitted only subsequently to the end of trial notification. The Sponsor should submit this report within one year from study termination.

14 CONFIDENTIALITY

This document contains trade secrets that are confidential and should not be made available to any third party. All individuals that attain knowledge of this protocol should be informed that the reported information is confidential and should not be further disclosed. Publication of the study results can only take place with written permission of the Sponsor.

15 PROTECTION OF PERSONAL DATA

Personal data will be collected and processed in full compliance with General Data Protection Regulation (EU) 2016/679 (GDPR) (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data

and on the free movement of such data (General Data Protection Regulation; OJ L 119, 4.5.2016, p.1). Furthermore, it is confirmed that data will not be transferred to third countries.

Personal data that will be collected in the study and will be pseudo-anonymously registered on coded Case Report Form (CRF) and used only for study purposes. The information collected will not disclose name or any other information (such as address, AMKA (Social security number), etc.) that could reveal subject's identity. All subjects will receive a "study code number" (pseudonymization) and only the authorized study personnel are able to associate this code with subject's identity. Sponsor and its delegated CRO will handle only data from the coded Case Report Form (CRF) that have only the "study code number" and in no way personal data that could reveal the identity of the subject will be transferred to them.

Data that will be recorded on CRF and will be processed for the procedures of the study include: a) sex, b) age, c) medical history, d) results of measurements during study visits. The purpose of processing these data is to draw conclusions for this clinical study.

Responsible for personal data handling (recording, transfer on CRF) is the Principal Investigator (PI). Personal data will only be handled by the Investigator and the authorized study personnel under his/her supervision. Responsible for the process of the coded data of CRFs (pseudonymized) on behalf of the Sponsor is the authorized CRO (BECRO Ltd.) and in particular the Data Management responsible, and the CRO (Product Life Science) for SAE management. According to GDPR, Data protection Officer (DPO) on behalf of the Sponsor has been assigned (dpo@unither-pharma.com).

There are no other recipients of personal data. Also, personal data that could reveal subject's identity will not be transferred to a third country (outside the European Economic Association) .

The scientific conclusions that will result from the study, any announcements in conferences or publications will be aggregation of all participants in the study and will not reveal any subject's identity. The same applies to public registers of studies (such as https://www.clinicaltrialsregister.eu, https://clinicaltrials.gov, the European Medicines Agency / EMA, the US Food and Drug Administration (FDA).

Data will be retained to fulfil the study purposes, including any relating to legal, or reporting requirements and will be archived for 25 years in accordance with the clinical study archiving guidelines or for as long as these guidelines demand in case of an amendment.

In order to ensure the quality of the clinical trial procedures, an authorized representative of the Sponsor, the Contract Research Organisation (CRO) and the supervising regulatory authorities will be allowed by the Principal Investigator to have access to the full data collected, including identification data during quality audits. During quality controls, these authorized representatives will use data only to verify that the clinical trial is conducted in accordance with the approved procedures and protocol and will not receive copies of the data collected. They will not use data for other purposes. All people who have access to data are trained professionals and are bound by

confidentiality and / or professional secrecy. In addition to quality controls, the Sponsor, CRO and supervising regulatory authorities will receive and process only pseudonymous data.

15.1 **Personal data breach**

Personal data breach" means "a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed".
Incidents under Articles 33 and 34 of the GDPR will not be considered personal data breaches if:

- They do not affect personal data, that is to say, data not related to identified or identifiable natural persons.
- They do not affect personal data processing performed by a data controller or a data processor.
- They have occurred during data processing carried out by a natural person in the course of a household activity.

A security incident that has not affected the personal data or personal data processing is not a personal data breach, given that no damages could arise for the rights and freedoms of natural persons whose data are subject to the processing, regardless of other damages that could occur for the data controller or the data processor.

15.2 **Prevention of Personal data breach**

The pseudonymisation of personal data that is implemented in the conduct of the study is a preventive measure for personal data breach.

15.3 **Measurements in case of Personal Data breach**

In the case of a personal data breach, the controller (CRO) must immediately inform the data protection officer (DPO) assigned by Sponsor (dpo@unither-pharma.com), or no later than 24 hours of detecting the breach. The CRO shall without undue delay and, where feasible, not later than 72 hours after having become aware of it, notify the personal data breach to the supervisory authority competent in accordance with Article 55 of the GDPR, unless the personal data breach is unlikely to result in a risk to the rights and freedoms of subjects (natural persons). Where the notification to the supervisory authority is not made within 72 hours, it shall be accompanied by reasons for the delay.

The notification shall at least:

- describe the nature of the personal data breach including where possible, the categories and approximate number of data subjects concerned and the categories and approximate number of personal data records concerned;

- communicate the name and contact details of the data protection officer or other contact point where more information can be obtained;
- describe the likely consequences of the personal data breach;
- describe the measures taken or proposed to be taken by the controller to address the personal data breach, including, where appropriate, measures to mitigate its possible adverse effects.

Where, and in so far as, it is not possible to provide the information at the same time, the information may be provided in phases without undue further delay.

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17 APPENDIX

17.1 Appendix – Names and Details of CRO and other sub-contractors

Unither-Pharmaceuticals has contracted with BECRO Ltd, CRO:

BECRO Ltd
registered office located at

GREECE
to conduct:

- Study procedure according to clinical study protocol
- The regulatory submission of this study to the local Ethics Committees and national competent authorities.
- The monitoring activities
- The data management
- The statistics
- The Clinical Study Report elaboration

UNITHER-Pharmaceuticals has contracted with PRODUCT LIFE SCIENCE, a CRO specialized in Vigilance and Medical Information activities:

PRODUCT LIFE SCIENCE
registered office located at
14 rue Gerty Archimède
75012 Paris
FRANCE

to conduct:

- The pharmacovigilance activities

UNITHER-Pharmaceuticals has contracted with EUROFINS CTS, a pharmaceutical company specializing in the field of packaging and distribution of drugs for clinical trials:

EUROFINS Clinical Trial Supplies
registered office located at
ZA du Charpenay,
10 rue de l'aqueduc
69210 LENTILLY
FRANCE
to conduct:

- Packaging activities
- IMP and Auxiliary product site distribution

17.2 **Appendix – SAE Forms**

Serious Adverse Event Report Form

Sponsor: UNITHER-Pharmaceuticals **Protocol n°: UP-CLI-2023-01**
Site N°: **Investigator:**

After completion of all pages, please transmit immediately this form, and attached documents, if any, to the following email:
safety@productlife-group.com or e-fax: +33(0)1 84 27 08 82

Sponsor: **Unither**	**Email : safety@productlife-group.com**		
	Clinical Project Manager *(Name)*:		
Principal Investigator *(Name)*:			
Protocol n°: **UP-CLI-2023-01** **(Mandatory)**	**Investigational product:** **(Mandatory)**	**Expeditor** *(Name)*: *Phone number:*	**Site Number:** **Country:**
Transmission date : |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* **(Mandatory)**			
Number of pages: (incl. this page)	**_____ Pages**		
Attached copies of completed CRF pages:	☐ Adverse events ☐ Medical History and pre-existing conditions ☐ Medications		

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**

This SAE report is : ☐ Initial report ☐ Follow-up report

Is the SAE aggravation of a pre-existing AE recorded in the CRF: ☐ Yes ☐ No
If yes, please put the number of AE: |__|__|

Category of SAE (*as applicable to study protocol)

Date when AE became serious if applicable : |__|__|/|__|__|__|/|__|__|__|__| *(dd/mmm/yyyy)*

☐ Death :
date of death |__|__|/|__|__|__|/|__|__|__|__|
(dd/mmm/yyyy)

☐ Life threatening situation

☐ Hospitalization or Prolongation of existing Hospitalization
Admission from : |__|__|/|__|__|__|/|__|__|__|__|
To : |__|__|/|__|__|__|/|__|__|__|__| *(dd/mmm/yyyy)*
☐ not discharged
Discharge summary available (provide copy) :
☐ Yes ☐ No

☐ Persistent or significant disability or incapacity
Specify: _____

☐ Congenital anomaly or birth defect
Specify: _____

☐ Other Important medical event*
Specify: _____

Patient

Patient ID : **(Mandatory)**
Randomization number :

Gender: ☐ M ☐ F
Date of Birth:
|__|__|/|__|__|__|/|__|__|__|__|
(dd/mmm/yyyy)
Or Age at time of event : |__|__|
Weight : |__|__|__|, |__|kg

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**

Investigational Product			
Investigational product: **(Mandatory)** Indication: Kit/ Batch/ lot Number:			Dose: |__|__| Unit :_____ Frequency: Route:
Information of study administration	From (dd/mm/yyyy) |__|__|/|__|__|/|__|__|__|__|	To (dd/mm/yyyy) |__|__|/|__|__|/|__|__|__|__|	☐ Ongoing at time of report
Action taken regarding IMP:	☐ NA (in case of single dose) ☐ None / Continued ☐ IMP reduced on date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* Did AE subsided? ☐ Yes ☐ No ☐ Unknown ☐ IMP Interrupted Stop date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* Did AE subsided? ☐ Yes ☐ No ☐ Unknown ☐ IMP Reintroduction date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* Did AE reappear after reintroduction? ☐ Yes ☐ No ☐ Unknown ☐ Patient permanently withdrawn from IMP due to this AE		
Study code broken	☐ Yes If yes, date : |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)*	☐ No	☐ Not Applicable (Open label)

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**

Description of Serious Adverse Event	
Nature of SAE (diagnosis or major symptom and/or sign):	
Description of SAE:	
Intensity of SAE: ☐ Mild ☐ Moderate ☐ Severe As defined in Protocol	
Event start date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* Time : |__|__| : |__|__| (Hours:Minutes)	Event end date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* Time : |__|__| : |__|__| (Hours:Minutes)
Relevant Tests / procedures / laboratory exams to confirm AE : ☐ No test performed ☐ Tests : _____ (provide copies)	

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**

Outcome of SAE for the Patient	Relationship to	
	Investigational product (Mandatory)	**Other causality factor ?**
☐ Not Recovered ☐ Recovering ☐ Recovered with sequelae, being: ..... Resolution date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* ☐ Recovered without sequelae Resolution date: |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* ☐ Fatal /Death |__|__|/|__|__|__||/|__|__|__|__| *(dd/mmm/yyyy)* ☐ Unknown	☐ Not related ☐ Unlikely related ☐ Possibly related ☐ Probably related ☐ Definitely related	☐ None ☐ Disease under study ☐ Past / current medical condition(s) ☐ Concomitant medications ☐ Drug-drug interactions ☐ Protocol-related procedure: specify: _____ ☐ Not protocol-related procedure: specify: _____ ☐ Other, specify: _____

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**

Relevant medical and surgical history / or copy of CRF pages (CRF page XXX) related to medical and surgical history :				☐ None
No.	**Disease or Surgery**	**Start date** *(dd/mmm/yyyy)*	**End Date** *(dd/mmm/yyyy)*	**Current medication?**
1		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
2		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
3		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
4		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
5		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
6		|__|__|/|__|__|__||/|__|__|__|__|	|__|__|/|__|__|__||/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**
Patient N°

Relevant medical and surgical history / or copy of CRF pages (CRF page XXX) related to medical and surgical history : ☐ None

No.	Disease or Surgery	Start date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Current medication?*
1		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
2		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
3		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
4		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
5		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No
6		|__|__|/|__|__|/|__|__|__|__| Or ☐ Ongoing	☐ Yes ☐ No

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N° **Investigator:**

Relevant Concomitant Medication						☐ None
No.	**Drug name (Trade name)**	**Indication for use**	**Dose description (Dose, Unit, Frequency)**	**Route (1)**	**Start Date (dd/mmm/yyyy) End Date (dd/mmm/yyyy)**	**Ongoing at the end of the study (2)**
1	....	....		/__/__/	Start |__|__|/|__|__|__|/|__|__|__|__| End |__|__|/|__|__|__|/|__|__|__|__|	☐
2	....	....		/__/__/	Start |__|__|/|__|__|__|/|__|__|__|__| End |__|__|/|__|__|__|/|__|__|__|__|	☐
3	....	....		/__/__/	Start |__|__|/|__|__|__|/|__|__|__|__| End |__|__|/|__|__|__|/|__|__|__|__|	☐
4	....	....		/__/__/	Start |__|__|/|__|__|__|/|__|__|__|__| End |__|__|/|__|__|__|/|__|__|__|__|	☐

*(1) **Route:** AU = Auricular; IA = Intra-Articular; SC = Subcutaneous; ID = Intradermal; IM = Intramuscular; IV = Intravenous; LO = Local/Topical; NA = Nasal. OP = Ophthalmic; PO = Oral; SL = Sub-Lingual; RE = Rectal, NK = Not Known; OT = Other.*
(2) If the treatment is ongoing at the end of the study, tick off the box. If not, write the end date.

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Investigator: **Site N°:**

Comments:

Completed by:			
Name	Position	Signature	Date
Investigator's signature (Mandatory)			
Name		Signature	Date

17.3 Appendix – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or

no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.