CLINICAL STUDY PROTOCOL

Study CRO-PK-20-343 - Sponsor code CHL.3-01-2020

A Phase I/II, randomized, placebo-controlled, double-masked, efficacy, safety and local tolerability study of Chloroprocaine 3% gel eye drops in healthy volunteers

Single dose, randomised, placebo-controlled, parallel-group, double-masked, efficacy, safety and local tolerability study

Test investigational product:	Chloroprocaine 3% ocular gel (30 mg/mL), Sintetica S.A., Switzerland
Control:	Placebo, vehicle for chloroprocaine 3% ocular gel, Sintetica S.A., Switzerland
Sponsor:	Sintetica S.A., Via Penate 5, 6850 Mendrisio, Switzerland Phone: +41.91.6404250 Fax: +41.91.6468561
Principal Investigator:	Milko Radicioni, MD - Principal Investigator CROSS Research S.A., Phase I Unit, Via F.A. Giorgioli 14 CH-6864 Arzo, Switzerland Phone: +41.91.64.04.450 Fax: +41.91.64.04.451 Email: clinic@croalliance.com
Development phase:	Phase I/II
Version and date:	Final version 1.0, 21FEB20

This study will be conducted in accordance with the current version of Good Clinical Practice (GCP), ICH topic E6 (R2)

This document comprises 54 pages

PROTOCOL APPROVAL

SPONSOR
Sintetica S.A., Switzerland

Sponsor representative
Elisabetta Donati, Corporate Director Scientific Affairs

25 FEB 2020 _____ _____
Date Signature

INVESTIGATORS

I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki, the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirements, including supervising any individual or party to whom I will delegate trial-related duties and functions at the trial site.

Principal Investigator
Milko Radicioni, MD
Phase I Clinical Unit, Arzo, Switzerland

24 FEB 2020 _____ M.R. _____
Date Signature

CRO
CROSS Research S.A., Switzerland

Coordination
Chiara Castiglioni, Clinical Project Leader and Senior CRA

24 FEB 2020 — Date
Chiara Castiglioni — Signature

Medical Writing Representative
Chiara Leuratti, Clinical Projects Unit Head

24 FEB 2020 — Date
Chiara Leuratti — Signature

Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head

24 FEB 2020 — Date
Alessandra Gentili — Signature

Quality Assurance Unit Representative
Mario Corrado, Quality Assurance Manager, Unit Head

25 FEB 2020 — Date
Mario Corrado — Signature

STUDY SYNOPSIS

Title: A Phase I/II, randomized, placebo-controlled, double-masked, efficacy, safety and local tolerability study of Chloroprocaine 3% gel eye drops in healthy volunteers
Protocol number: CRO-PK-20-343 / Sponsor code CHL.3-01-2020
Clinical phase: Phase I/II
Study design: Single dose, randomised, placebo-controlled, parallel-group, double-masked, efficacy, safety and local tolerability study
Planned nr. of centres / countries: One/Switzerland
Principal Investigator and study centre: Milko Radicioni, MD; CROSS Research S.A., Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Investigational product(s): TEST (T): Chloroprocaine 3% ocular gel (30 mg/mL), Sintetica S.A., Switzerland Control (P): Placebo, vehicle for chloroprocaine 3% ocular gel, Sintetica S.A., Switzerland
Auxillary meidicinal product (AxMP) Fluoresceine-Oxybuprocaine SDU Faure (Omnivision, Neuhausen)
Dose regimen(s): One hundred and five (105) healthy male and female subjects will be randomised in a 4:1 ratio to receive a single ocular instillation of Chloroprocaine 3% ophthalmic gel or matching placebo (vehicle) (84 subjects will receive chloroprocaine and 21 subjects will receive placebo). The assigned investigational product (3 drops) will be instilled in the right eye of each subject. Administrations will be performed at the clinical centre by the Investigator or his deputy on study day 1. For each administration, the 3 drops will be instilled at a 1 min ± 15 sec interval.
Definitions: Time 0h (T0) is defined as the time of the end the last drop (drop 3) instillation. Pre-dose (baseline) assessments are performed before the first drop instillation. Post-dose times are calculated from T0, i.e. from the end of the instillation of the last drop (drop 3).
Objectives: The objective of the study is to evaluate the efficacy, safety and local tolerability of Chloroprocaine 3% ophthalmic gel as compared to matching placebo in healthy subjects.
End-points: **Primary end-point:** Proportion of subjects gaining full conjunctival anesthesia of the ocular surface, evaluated by conjunctiva pinching (0.3-mm forceps), 5 minutes after administration of Chloroprocaine 3% ophthalmic gel, in comparison to placebo - only study eye (right eye) **Secondary end-points:** ➢ Time to anesthesia, evaluated by conjunctiva pinching (0.3-mm forceps) - only study eye (right eye) ➢ Duration of anesthesia, evaluated by conjunctiva pinching (0.3-mm forceps) - only study eye (right eye) ➢ Visual acuity – both eyes ➢ Ocular symptoms (burning, stinging, itching, foreign body sensation) evaluated using a 0-100 mm VAS - both eyes ➢ Objective ocular signs (Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) by Slit lamp examination - both eyes ➢ Corneal fluorescein staining by slit lamp examination - both eyes ➢ Intraocular pressure (IOP) - both eyes ➢ Fundus ophthalmoscopy (vitreous, macula, retina and optic nerve head) with the slit lamp - both eyes ➢ Treatment-emergent adverse events (TEAEs), assessed throughout the study ➢ Vital signs (blood pressure and heart rate)

STUDY SYNOPSIS (cont.)

Study variables:
Primary variable:
Conjunctival anaesthesia evaluation by conjunctival pinching (with 0.3 mm forceps) at 5 min post-dose (see below) - only study eye (right eye)
Secondary variables:
- Conjunctival anaesthesia evaluation by conjunctival pinching (with 0.3 mm forceps) at the pre-specified assessment time-points (see below) - only study eye (right eye)
- Ocular symptoms (burning, stinging, itching, foreign body sensation) using a 0-100 mm VAS - both eyes
- Visual acuity (EDTRS chart) – both eyes
- Objective ocular signs (Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) by SLE - both eyes
- Corneal fluorescein staining by SLE - both eyes
- Intraocular pressure (IOP) - both eyes
- Fundus ophthalmoscopy (vitreous, macula, retina and optic nerve head) with the slit lamp - both eyes
- Treatment-emergent adverse events (TEAEs), assessed throughout the study
- Vital signs (blood pressure and heart rate)

Anaesthesia evaluation:
Anaesthesia will be tested by conjunctival pinching (with 0.3 mm forceps) at 20, 40 and 60 seconds. The evaluation will be performed again at 5 min post-dose. If anaesthesia is already present at 20 and 40 seconds, pain will not be assessed at 60 sec but directly at 5 minutes. Further assessments will be performed every 5 min up to 60 min post-dose. Alternatively, if the subject experiences pain at two consecutive assessments, pinching will be suspended and the subsequent assessment will not be performed. If the subject experiences pain at 5 minutes, no more testing will be performed and the subject will be considered not to have gained anaesthesia.

Safety and tolerability assessments: Physical examinations at screening and final visit; adverse events (AE) recording throughout the study; vital signs (blood pressure and heart rate) at screening, pre-dose, post-dose and at follow-up or early termination visit (ETV); urine pregnancy test for women at screening; corneal fluorescein staining, IOP and fundus ophthalmoscopy at screening and follow-up/ETV. Ocular symptoms and SLE (excluding corneal fluorescein staining) at screening, pre-dose, post-dose and at follow-up/ETV

Sample size:
A total of 105 healthy men and women will be included in the study. Active vs. placebo treatment will have a 4:1 ratio.
Initially, local tolerability and safety will be evaluated on the first 20 enrolled subjects (16 treated with chloroprocaine 3% ocular gel and 4 with placebo).
After the first 20 subjects have completed the study, local tolerability and safety data will be evaluated and if treatment safety is confirmed, efficacy, beside local tolerability and safety, will be assessed on the 85 subsequent subjects (68 active gel and 17 with placebo).

Sample size for the efficacy evaluation was formally calculated as follows:
Sample size per group was calculated by comparing two independent proportions (experimental and placebo success rate) with a two-sided alpha=0.05 and a power of 0.95. This is based on the assumption, that the experimental success rate is 80% and the vehicle success rate is 30%, taking a dropout rate of 20% into account. For sample size estimation, NQuery (Version 4.0) was used implementing formulas described in Chow et al (2008).

Main selection criteria:
Inclusion criteria:
1. *Informed consent*: Signed written informed consent before inclusion in the study
2. *Sex and age*: Healthy men and women, 18 - 55 years inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: Systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study

STUDY SYNOPSIS (cont.)

Main selection criteria, continued:

Inclusion criteria, continued:

6. *Contraception and fertility*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit;
   b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   c. A male sexual partner who agrees to use a male condom with spermicide
   d. A sterile sexual partner

   Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. For all women, urine pregnancy test result must be negative at screening.

Exclusion criteria:

1. *Physical findings*: Clinically significant abnormal physical findings which could interfere with the objectives of the study
2. *Visual acuity*: Best corrected visual acuity < 1/10
3. *Concomitant medications*: Medications, including over the counter medications and herbal remedies, systemic opioids and morphine drugs, topical ocular products with anaesthetic action, systemic analgesic drugs, for 2 weeks before study screening
4. *Ophthalmic diseases*: Clinically significant ocular disease; eye movement disorder (i.e. nystagmus); dacryocystitis and all others pathologies of tears drainage system; corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration and superficial punctuate keratitis); history of inflammatory ocular disease (iritis, uveitis, herpetic keratitis), history of ocular traumatism, infection or inflammation within the last 3 months or history of any other ocular disease that may affect the outcome of the study or the subject's safety
5. *Ophthalmic surgery*: History of ophthalmic surgical complications (e.g. cystoid macular oedema) in the last 6 months
6. *Diseases*: Significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, psychiatric or neurological diseases or surgeries that may interfere with the aim of the study
7. *Allergy*: Ascertained or presumptive hypersensitivity to the active principle and/or ingredients of investigational products; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
8. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. *Alcohol test*: positive alcohol breath test at Day 1
11. *Pregnancy (women only)*: positive or missing pregnancy test at screening, pregnant or lactating women

STUDY SYNOPSIS (cont.)

Schedule:		
	Day	**Procedures/Assessments**
Screening – Visit 1	*Day -21 / Day - 1*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data ➢ Ocular medical and surgical history ➢ Other medical and surgical history ➢ Previous and concomitant medications ➢ Physical examination (including ocular examination, body weight, height) ➢ Vital signs (blood pressure and heart rate) check ➢ Urine pregnancy test for women ➢ Adverse event (AE) monitoring ➢ Ocular symptoms (0-100 mm VAS) - all subjects - both eyes ➢ Visual acuity (EDTRS) – both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - all subjects - both eyes ➢ Corneal fluorescein staining with SLE - all subjects - both eyes ➢ Intraocular pressure measurement - all subjects - both eyes ➢ Fundus ophthalmoscopy (with slit lamp) - all subjects -both eyes ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation
Visit 2	*Day 1*	➢ Alcohol test ➢ Inclusion/exclusion criteria evaluation ➢ Subject eligibility confirmation ➢ Enrolment and randomisation ➢ Vital signs (blood pressure, heart rate) check - pre-dose - all subjects ➢ Ocular symptoms (0-100 mm VAS) - pre-dose - all subjects - both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - pre-dose - all subjects - both eyes ➢ Instillation of the investigational product (right eye only) ➢ Assessment of conjunctival anaesthesia by conjunctival pinching (0.3 mm forceps) at the pre-specified post-dose assessment times - ***efficacy evaluation subjects only - study eye only (right eye)*** ➢ Ocular symptoms (0-100 mm VAS) - at the end of the study day - all subjects - both eyes ➢ Vital signs (blood pressure, heart rate) check - at the end of the study day - all subjects ➢ Slit lamp examination - at the end of the study day (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - all subjects - both eyes ➢ AE and concomitant medications (throughout the study day)
Visit 3	*Day 2 - Phone call*	➢ AE and concomitant medications check

STUDY SYNOPSIS (cont.)

Schedule, continued:		
Visit 4	*Day 7±1 Follow up*	➢ AE and concomitant medications ➢ Vital signs (blood pressure, heart rate) check ➢ Physical examination ➢ Ocular symptoms (0-100 mm VAS) - both eyes ➢ Visual acuity (EDTRS) – both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - both eyes ➢ Corneal fluorescein staining (with SLE) - both eyes ➢ Intraocular pressure measurement - both eyes ➢ Fundus ophthalmoscopy (with slit lamp) - all subjects - both eyes

Data analysis:

The statistical analysis of efficacy and safety/tolerability data will be performed using SAS® version 9.3 (TS1M1) or higher. The data documented in this study will be summarised using classic descriptive statistics, i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables. Not available data will be evaluated as "missing values".

Primary anaesthesia results will be coded as success/failure, listed by subject and summarized using contingency tables overall and by treatment group. Resulting proportions will be presented with 95% confidence interval. The 2 groups will be compared using Pearson's χ^2 test. The null hypothesis of equal success between the 2 treatment arms at the α=0.05 level will be rejected if:

$$\left| \frac{\widehat{p_1} - \widehat{p_2}}{\sqrt{\frac{\widehat{p_1}(1-\widehat{p_1})}{n_1} + \frac{\widehat{p_2}(1-\widehat{p_2})}{n_2}}} \right| > Z_{\alpha/2}$$

where p_1 is the proportion of subjects who meet the primary endpoint in the active group, while p_2 is the proportion of subject who meet the primary endpoint in the vehicle group.

Time to anesthesia and duration of anesthesia will be listed and summarized overall and by group using descriptive statistics (mean, median, standard deviation, minimum, maximum, 95% confidence interval on the mean, and number of observations). The 2 groups will be compared using non-parametric Mann-Whitney's test for continuous variables.

STUDY SCHEDULE

ACTIVITIES	Screening	Intervention and assessments	Telephone call	Follow-up/ETV[5]
Visit	**V1**	**V2**	**V3**	**V4**
	Day -21 / -1	**Day 1**	**Day 2**	**Day 7±1**
Informed consent	x			
Demography	x			
Ocular medical and surgical history	x			
Other medical and surgical history	x			
Physical examination	x			x
Previous medications	x			
Concomitant medications	x	x	x	x
Height	x			
Body Weight	x			
Body mass index	x			
Alcohol test		x		
Vital signs (blood pressure, heart rate) check[1]	x	x		x
Urine pregnancy test (women)	x			
Ocular symptoms (0-100 mm VAS)[1,2]	x	x		x
Slit lamp examination[1,2]	x	x		x
Corneal fluorescein staining[2]	x			x
Intraocular pressure[2]	x			x
Fundus ophthalmology[2]	x			x
Visual acuity (EDTRS)[2]	x			x
Inclusion / exclusion criteria check	x	x		
Subject eligibility	x	x		
Enrolment and randomisation		x		
Investigational product administration[3]		x		
Conjunctival pinching[4]		x		
Adverse events monitoring[6]	x	x	x	x

1. *At screening, on day 1 at pre-dose and at the end of the study day, and at follow-up/ETV*
2. *Both eyes*
3. *On day 1, after pre-dose (baseline) assessments*
4. *Study eye (right eye) only - On day 1, at 20, 40 and 60 seconds and then at 5-min intervals up to 60 min post-dose, as applicable (please refer to CSP main text).*
5. *Early termination visit (ETV) in case of premature discontinuation*
6. *AEs monitored starting at the screening visit, immediately after informed consent, up to the follow-up visit/ETV.*

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AxMPs	Auxillary meidicinal products
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPL	Clinical Project Leader
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CRS	Clinical Study Report
CS	Clinically Significant
CV	Coefficient of Variation
EC	Ethics Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IOP	Intraocular pressure
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intra-Uterine Device
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
P	Placebo solution
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Event
SLE	Slit lamp examination
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test
TEAE	Treatment-Emergent Adverse Event
USDA	United States Department of Agriculture
VA	Visual Acuity
VAS	Visual Analogue Scale
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

Safe and efficient topical local anaesthesia is crucial for surgical procedures in ophthalmology, such as cataract surgery, intravitreal injections, refractive surgery or others. The development of less invasive surgical techniques, which allow for most interventions to be performed as outpatient surgeries, has stimulated the development of new approaches in topical anaesthesia. Currently, oxybuprocaine, lidocaine or tretracaine - mostly formulated as liquid eye drops - are used to provide local anesthesia of the eye (1). However, it has been hypothesized that formulations with optimized physical and chemical properties such as high viscosity gel based formulations might be superior to eye drops in terms of efficacy and safety.

1.1.1 Background on Chloroprocaine

Chloroprocaine is a local anaesthetic that has been widely used in the past for spinal anaesthesia by intrathecal administration (2). Chloroprocaine, like other local anesthetics in this group, reduces signal conduction in neurons by altering the Na^+ channels in the neuronal cell membrane responsible for the action potential propagation. Pharmacologically speaking, one of the key advantages of Chloroprocaine is the fast onset (usually within minutes) and the fast metabolization by ester hydrolysis, which leads to a very short plasma half-life of less than 30 seconds. This leads to good controllability and also high concentrations can be used with minimal risk of toxicity. As such, Chloroprocaine is the ideal anaesthetic for regional anesthesia in patients undergoing short-duration surgeries, providing rapid onset of action, adequate potency, predictable duration, fast recovery, and a safe toxicological profile when compared to other local anesthetics.
The current study aims to investigate the efficacy, safety and local tolerability of a newly developed Chloroprocaine ophthalmic gel in humans. Based on theoretical considerations, one can hypothesize that a gel formulation could provide additional benefits compared to a drop solution. First, because of its high viscosity, gel formulations stay longer on the ocular surface and may therefore provide a longer anesthetic effect. Secondly, because of the gel nature of the formulation, the drainage of the drug through the nasolacrimal drainage system is reduced, which might limit absorption through the nasal mucosa and thus lead a low systemic exposure of the drug.

1.1.1.1 Regulatory status of Chloroprocaine

Chloroprocaine has been marketed since 1955 in the USA and Canada for epidural anaesthesia and peripheral blocks (Nesacaine® 1%, 2%, 3% injection). In the European Community, Chloroprocaine has received marketing authorization (Ampres® 10 mg/ml Injektionslösung) for spinal anesthesia in adults where the planned surgical procedure should not exceed 40 minutes. An extension application for the existing marketing authorization (new strength of 20 mg/ml, new route of administration: perineural anesthesia) is currently under review.

1.1.2 Non-clinical development

As Chloroprocaine has been widely used in the past and holds a marketing authorization for spinal anesthesia via intrathecal administration, the toxicological profile is well described. Animal studies report a good safety profile and no particular sign of systemic toxicity beside those already known for this class of local anesthetics. For more details on systemic toxicology please refer to the Investigator's Brochure.

1.1.2.1 Non-clinical safety and Toxicology on the eye

Local tolerability and safety and proof-of-concept of Chloroprocaine 3% eye drops was investigated in a non-clinical development program. Data of a GLP ocular irritation study in rabbits report good tolerability of the formulation on the ocular surface (3). Further, a 7-day GLP local tolerance study including histopathological assessments in rabbits confirms good tolerance on the ocular surface (4). A non-GLP efficacy study performed in a rabbit animal model supports the concept of Chloroprocaine 3% ophthalmic gel (5), showing an anaesthetic effect up to 60 minutes after instillation depending on the viscosity of the gel formulation. An in-depth description of the non-clinical development program is given in the Investigator´s Brochure.

1.2 Rationale of the study

Scientific advice on the planned clinical development plan has been obtained from the FDA in Sept. 2019 and from the Federal Institute for Drugs. As part of this development plan, and following the advice of the competent authority, a combined phase I/II study will be performed as described here in this protocol. In addition, a phase II/III study in healthy volunteers is planned to be performed in Austria.

In the present study, the efficacy, safety and tolerability of Chloroprocaine 3% ophthalmic gel for topical anaesthesia of the eye will be evaluated in healthy subjects. Based on theoretical assumptions it is reasonable to expect that the formulation under study offers significant advantages compared to currently available formulations. Most importantly, because of its gel nature it should stay longer on the ocular surface than commonly used eye drops due to its viscosity and should not be drained by the punctae as quickly as drops with low viscosity (6). Due to its high viscous nature, the formulation systemic absorption through the nasolacrimal system is expected to be low, therefore reducing the potential for systemic toxicity.

The study will enrol a total of 105 healthy men and women. Safety and local tolerability data will be collected on the first 20 randomised subjects and evaluated. If safety and local tolerability is confirmed after the first enrolled subjects, the study will continue with the following 85 men and women on which treatment efficacy as well as safety and local tolerability will be assessed.
The rationale for dose selection is also presented in § 4.2.

1.3 Benefit/risk assessment

There is no direct benefit for the subjects under study. However, the findings of this study will help in assessing the safety, tolerability and efficacy of the ophthalmic Chloroprocaine 3% gel.

Chloroprocaine has been used for spinal anaesthesia for several years and is well tolerated. Chloroprocaine 3% ophthalmic gel is intended to be used for topical anaesthesia for patients undergoing eye surgery in the future. Due to its viscosity the gel tends to stay on the eye for a longer time than eye drops and should not be absorbed by the punctae as quickly as the tears. Thus, systemic absorption through the nasolacrimal system should be reduced, therefore reducing the potential for systemic toxicity.

Data from the non-clinical development program reports good local tolerability of Chloroprocaine 3% ophthalmic gel on the ocular surface. Further, non-clinical data from a proof-of-concept study indicates a strong and long-lasting anesthetic effect of Chloroprocaine 3% ophthalmic gel.

However, at this stage of development, local toxicity of Chloroprocaine 3% Gel in human eyes cannot be ruled out but the risk is considered low based on the safety factor calculated using preclinical data. Considering the expected low systemic exposure, systemic side effects are unlikely to occur. The most common systemic side effect that was observed after intrathecal injection was systemic hypertonia. Although it is unlikely to occur after ophthalmic use, in the present study blood pressure and heart rate will be assessed before after investigational products administration.

2 STUDY OBJECTIVES

The objective of the study is to evaluate the efficacy, safety and local tolerability of Chloroprocaine 3% ophthalmic gel as compared to matching placebo in healthy subjects.

2.1 Primary end-point

Proportion of subjects gaining full conjunctival anesthesia of the ocular surface, evaluated by conjunctiva pinching (0.3-mm forceps), 5 minutes after administration of Chloroprocaine 3% ophthalmic gel, in comparison to placebo - only study eye (right eye).

2.2 Secondary end-points

- Time to anesthesia, evaluated by conjunctiva pinching (0.3-mm forceps) - only study eye (right eye)
- Duration of anesthesia, evaluated by conjunctiva pinching (0.3-mm forceps) - only study eye (right eye)
- Visual acuity – both eyes
- Ocular symptoms (burning, stinging, itching, foreign body sensation) evaluated using a 0-100 mm VAS - both eyes
- Objective ocular signs (Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) by Slit lamp examination - both eyes
- Corneal fluorescein staining by slit lamp examination - both eyes
- Intraocular pressure (IOP) - both eyes
- Fundus ophthalmoscopy (vitreous, macula, retina and optic nerve head) with the slit lamp - both eyes
- Treatment-emergent adverse events (TEAEs), assessed throughout the study
- Vital signs (blood pressure and heart rate)

3 CLINICAL SUPPLIES

3.1 Treatment

3.1.1 Description of products

The analytical certificates will be supplied with the investigational products.

3.1.1.1 Test product

TEST (T)

Investigational product	Chloroprocaine 3% ocular gel, Sintetica S.A., Switzerland
Manufacturer	Unither Pharmaceuticals, France
Pharmaceutical form	Ocular gel
Dose	3 drops
Administration route	Ocular instillation

3.1.1.2 Control

Placebo (P)

Investigational product	Placebo, Vehicle for chloroprocaine 3% ocular gel, Sintetica S.A., Switzerland
Manufacturer	Unither Pharmaceuticals, France
Pharmaceutical form	Ocular gel
Dose	3 drops
Administration route	Ocular instillation

3.1.1.3 Auxilliary medicinal product

Fluoresceine-Oxybuprocaine SDU Faure (Omnivision, Neuhausen).

3.1.2 Dose regimen

One hundred and five (105) healthy male and female subjects will be administered by ocular instillation a single dose (3 drops) of Chloroprocaine 3% ophthalmic gel or matching placebo (vehicle) in a 4:1 ratio, according to the parallel-group randomised study design.

3.1.3 Route and method of administration

The assigned investigational product (3 drops) will be instilled in the right eye of each subject. Administrations will be performed at the clinical centre by the Investigator or his deputy on study day 1. For each administration, subsequent drops will be instilled at a 1 min ± 15 sec interval.

Definitions:
Time 0h (T0) is defined as the time of the end the last drop (drop 3) instillation.
Pre-dose (baseline) assessments are performed before the first drop instillation.

Post-dose times are calculated from T0, i.e. from the end of the instillation of the last drop (drop 3).

3.1.4 Investigational product distribution

The two investigational products will be administered by the Investigator or by his deputy. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

3.2 Packaging and labelling

Packaging and labelling of the investigational products will be carried out by the Sponsor. The primary packaging of the investigational products will be a 0.9-mL sterile gel presented in polyethylene blow-fill-seal vials packed in individual carton packages (subjects' kits).

Labelling in local language will report all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in "The rules governing medicinal products in the European Community", Volume 4).

Labelling on packages will report:

a) Name, address and telephone number of the Sponsor and CRO;
b) Pharmaceutical dosage form, route of administration, quantity of dosage units, the name/identifier and strength/potency;
c) Batch number;
d) Study Nr.;
e) The study subject identification number;
f) Expiry in month/year format and in a manner that avoids any ambiguity;
g) Investigator's name;
h) Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product);
i) "For clinical trial use only" or similar wording;
j) The storage conditions;
k) "Keep out of reach of children".

3.3 Storage conditions

The investigational products will be stored at 15-25°C in a dry locked place, sheltered from light. The products will not be refrigerated or frozen.

3.4 Drug accountability

The investigational products will be provided directly to the Investigator/clinical centre by the Sponsor, in excess of the amount necessary for the study (at least 25% excess).

After receipt of the investigational products' supply, the Investigator/pharmacist will confirm in writing by signing and dating standard drug accountability forms.

At the end of the study, used, unused and partially used supplies of the investigational products provided by the Sponsor will either be destroyed on site (upon written authorisation) or returned to the Sponsor, after assessment of drug accountability.

4 INVESTIGATIONAL PLAN

4.1 Overall study design

This is a phase I/II, single dose, randomised, placebo-controlled, parallel-group, double-masked, efficacy, safety and local tolerability study

4.2 Discussion of design

This study will be performed as part of a clinical development program for Chloroprocaine 3% ophthalmic gel, following scientific advice obtained from the FDA in Sept. 2019. As part of this development plan, and following the advice of the competent authority, beside the present study, a phase II/III study in healthy volunteers is planned to be performed in Austria.

The study will enrol a total of 105 healthy men and women. According to the study design, initially safety and local tolerability will be evaluated on the data collected for the first 20 randomised subjects (16 treated with the active product and 4 with placebo). For these subjects, no efficacy evaluation will be carried out. If safety and local tolerability are confirmed after the first enrolled subjects, the study will continue with the following 85 men and women (68 treated with the active product and 17 with placebo) on which treatment efficacy as well as safety will be assessed.

Each randomised subject will be allocated to a treatment group according to a computer generated randomisation list and a 4: 1 ratio for active treatment vs. placebo (see § 8.1). The study will be double-masked and the two investigational products will be indistinguishable.

The selected dose of Chloroprocaine gel is derived from animal data. In an ocular tolerance study (4) on New Zealand White Rabbits a 5 day 5times daily administration of Chloroprocaine ophthalmic gel was in general well tolerated. A transient absence of pupillary reflex and partial mydriasis were observed for eyes treated with Chloroprocaine 3% gel after each last daily administration. In summary, five daily instillations over 5 days of Chloroprocaine gel 3% in the right eyes of albino rabbits were both macroscopically and microscopically well tolerated.
A non-clinical dose finding study investigating Chloroprocaine 5% gel, Chloroprocaine 3% high viscosity gel and Chloroprocaine 3% low viscosity gel was performed on New Zealand White rabbits (Study number: A66C06315). Whereas Chloroprocaine 5% gel showed only limited tolerability on the ocular surface and was therefore not further investigated, Chloroprocaine 3% showed good tolerability together with a long anaesthetic effect (up to 60 minutes for the high viscosity gel, up to 45 minutes for the low viscosity gel). Based on this data, Chloroprocaine 3% high viscosity gel was chosen for further development. The performance of the selected formulation (Chloroprocaine 3% high viscosity gel) was then confirmed in a further study in group of 6 albino rabbits (7), again showing a good anaesthetic effect of Chloroprocaine 3% gel.

5 STUDY POPULATION

5.1 Target population

Healthy male and female subjects, aged 18-55 years inclusive

5.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and age*: Healthy men and women, 18 - 55 years inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study
6. *Contraception and fertility*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit;
   b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   c. A male sexual partner who agrees to use a male condom with spermicide
   d. A sterile sexual partner

   Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. For all women, urine pregnancy test result must be negative at screening.

5.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

1. *Physical findings*: Clinically significant abnormal physical findings which could interfere with the objectives of the study
2. *Visual acuity*: Best corrected visual acuity < 1/10
3. *Concomitant medications*: Medications, including over the counter medications and herbal remedies, systemic opioids and morphine drugs, topical ocular products with anaesthetic action, systemic analgesic drugs, for 2 weeks before study screening
4. *Ophthalmic diseases*: Clinically significant ocular disease; eye movement disorder (i.e. nystagmus); dacryocystitis and all others pathologies of tears drainage system; corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal

ulceration and superficial punctuate keratitis); history of inflammatory ocular disease (iritis, uveitis, herpetic keratitis), history of ocular traumatism, infection or inflammation within the last 3 months or history of any other ocular disease that may affect the outcome of the study or the subject's safety

5. *Ophthalmic surgery*: History of ophthalmic surgical complications (e.g. cystoid macular oedema) in the last 6 months
6. *Diseases*: Significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, psychiatric or neurological diseases or surgeries that may interfere with the aim of the study
7. *Allergy*: Ascertained or presumptive hypersensitivity to the active principle and/or ingredients of investigational products; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
8. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020 (8)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. *Alcohol test*: positive alcohol breath test at Day 1
11. *Pregnancy (women only)*: positive or missing pregnancy test at screening, pregnant or lactating women

5.3.1 Not allowed treatments

Any medications, including OTC and herbal remedies, in particular systemic opioids and morphine drugs, topical ocular products with anaesthetic action and systemic analgesic drugs, will NOT be allowed for 2 weeks before the start of the study and during the whole study duration. Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the Investigator’s opinion. Hormonal contraceptives will be allowed.

The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the Investigator, together with the Sponsor, considers it could affect the study assessments or outcome

6 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

6.1 Study visits and procedures

Each study subject will undergo 4 visits.

The study protocol foresees 1 period for each subject. Maximum study duration will be 29 days, screening visit and follow-up included. A written informed consent will be obtained before any study assessment or procedure.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical centre by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: day -21 / day -1

- **Interventional phase**
  - Visit 2: day 1

- **Final phase**
  - Visit 3: day 2: Telephone call
  - Visit 4: day 7 ± 1 or at early discontinuation: follow-up/early termination visit (ETV).

The schedule of the study procedures and assessments is presented below:

Schedule:

	Day	**Procedures/Assessments**
Screening – Visit 1	*Day -21 / Day -1*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data ➢ Ocular medical and surgical history ➢ Other medical and surgical history ➢ Previous and concomitant medications ➢ Physical examination (including ocular examination, body weight, height) ➢ Vital signs (blood pressure and heart rate) check ➢ Urine pregnancy test for women ➢ Adverse event (AE) monitoring ➢ Ocular symptoms (0-100 mm VAS) - all subjects - both eyes ➢ Visual acuity (EDTRS) – both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - all subjects - both eyes ➢ Corneal fluorescein staining with SLE - all subjects - both eyes ➢ Intraocular pressure measurement - all subjects - both eyes ➢ Fundus ophthalmoscopy (with slit lamp) - all subjects - both eyes ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation
Visit 2	*Day 1*	➢ Alcohol test ➢ Inclusion/exclusion criteria evaluation ➢ Subject eligibility confirmation ➢ Enrolment and randomisation ➢ Vital signs (blood pressure, heart rate) check - pre-dose - all subjects ➢ Ocular symptoms (0-100 mm VAS) - pre-dose - all subjects - both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - pre-dose - all subjects - both eyes ➢ Instillation of the investigational product (right eye only) ➢ Assessment of conjunctival anaesthesia by conjunctival pinching (0.3 mm forceps) at the pre-specified post-dose assessment times - ***efficacy evaluation subjects only - study eye only (right eye)*** ➢ Ocular symptoms (0-100 mm VAS) - at the end of the study day - all subjects - both eyes ➢ Vital signs (blood pressure, heart rate) check - at the end of the study day - all subjects ➢ Slit lamp examination - at the end of the study day (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - all subjects - both eyes ➢ AE and concomitant medications (throughout the study day)
Visit 3	*Day 2 - Phone call*	➢ AE and concomitant medications check

Schedule, continued:

	Day	Procedures/Assessments
Visit 4	*Day 7 ± 1* *Follow up*	➢ AE and concomitant medications ➢ Vital signs (blood pressure, heart rate) check ➢ Physical examination ➢ Ocular symptoms (0-100 mm VAS) - both eyes ➢ Visual acuity (EDTRS) – both eyes ➢ Slit lamp examination (SLE; Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) - both eyes ➢ Corneal fluorescein staining (with SLE) - both eyes ➢ Intraocular pressure measurement - both eyes ➢ Fundus ophthalmoscopy (with slit lamp) - all subjects - both eyes

6.2 Diet and lifestyle

Not applicable.

7 DESCRIPTION OF SPECIFIC PROCEDURES

7.1 Physical examination

Physical examinations, including ocular examinations, will be performed at the screening and final visit/ETV. Information about the physical examination will be recorded by the Investigator. Any abnormalities will be recorded.

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see § 11), will be recorded in the subject source documents.

Date of the physical examination, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.

7.1.1 Body weight

Body weight will be recorded at the screening visit. Subjects will be weighed (kg) lightly clothed without shoes. Height will also be measured at screening and BMI will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

7.1.2 Vital signs

Subjects blood pressure and heart rate will be measured by the Investigator or his/her deputy after 5 min at rest at the screening visit, on day 1 at pre-dose and at the end of the study day and at follow-up/ETV.

7.1.3 Alcohol test

An alcohol test will be performed on Day 1.

7.2 Ocular assessments

7.2.1 Ocular symptoms assessment

The following ocular symptoms will be assessed: burning, stinging, itching, foreign body sensation.

Scores will be determined using a 100 mm VAS where 0 means "no symptoms" and 100 means "worst possible discomfort".

The assessments will be performed for all subjects and both eyes at the screening visit, on day 1 at pre-dose and at the end of the study day and at follow-up/ETV.

7.2.2 Visual acuity

Visual acuity will be assessed, for all subjects and both eyes, at the screening visit and at follow-up/ETV, using an EDTRS chart.

7.2.3 Slit lamp examination

Slit lamp biomicroscopy will be performed for the assessment of the following parameters: conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling.
Presence and severity will be graded according to a 4 point scale, where (0) none, (1) mild, (2) moderate, (3) severe.

The assessment will be performed for all subjects and both eyes at the screening visit, on day 1 at pre-dose (baseline) and study day end and at follow-up/ETV.

7.2.4 Corneal fluorescein staining

Fluorescein (see § 3.1.1.3) will be used to detect corneal epithelial defects using slit lamp biomicroscopy. As grading scale for corneal damage, the NEI/Industry Workshop guidelines will be used (9). The cornea will be divided into five sectors (central, superior, inferior, nasal and temporal), each of which is scored on a scale of 0–3, where 0 means no staining and 3 means maximum staining, with a maximal score of 15.

Corneal fluorescein staining will be performed for all subjects and both eyes at the screening visit and at follow-up/ETV.

7.2.5 Assessment of conjunctival anaesthesia

Conjunctival anaesthesia will be assessed in the study eye only (right eye) by pinching of the conjunctiva with 0.3-mm forceps. Subjects will be asked to immediately report if they feel pain (***efficacy evaluation subjects only***).

Subjects will initially be tested at 20 seconds, 40 seconds, and 60 seconds post-dose (day 1).

The evaluation will be performed again at 5 min post-dose. If anaesthesia is already present at 20 and 40 seconds, pain will not be assessed at 60 sec but directly at 5 minutes. Further assessments will be performed every 5 min up to 60 min post-dose. Alternatively, if the subject experiences pain at two consecutive assessments, pinching will be suspended and the subsequent assessment will not be performed. If the subject experiences pain at 5 minutes, no more testing will be performed and the subject will be considered not to have gained anaesthesia. (10).

7.2.6 Fundus ophthalmology

Indirect fundus ophthalmoscopy will be performed, for all subjects and both eyes, at the slit lamp using a +90 diopters Volk lens (11), at the screening visit and at follow-up/ETV.

7.2.7 Intraocular pressure

Intraocular pressure will be measured with a slit-lamp mounted Goldmann applanation tonometer. Before each measurement one drop of oxybuprocaine hydrochloride combined with sodium fluorescein will be used for local anaesthesia of the cornea.

The assessment will be performed for all subjects and both eyes at the screening visit and at follow-up/ETV.

8 ASSIGNMENT OF STUDY TREATMENT

8.1 Randomisation

The randomisation list will be computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of the SAS® version 9.3 (TS1M1) (12) or higher (the actual version will be stated in the final report). The randomisation list will be attached to the final clinical study report.

8.2 Treatment allocation

Subjects will be assigned to one of the two treatment groups (Choroprocaine/placebo) in a 4:1 ratio according to the randomisation list. A randomisation number will be given to the subjects on study day 1 in chronological order, after eligibility confirmation.

8.3 Blinding

The study will be carried out in a double-masked (double-blind) fashion, therefore the Investigator/deputy administering the investigational products, the ophthalmologists performing the measurements as well as the study participants will not know the allocated product.

Three (3) copies of the randomisation list will be generated and sealed in individual envelopes:

- one copy will be sent to the manufacturer for the preparation of the individual treatment boxes
- one copy will be kept at the CRO Quality Assurance Unit
- one copy will be stored in the statistical study file

Neither the members of the clinical unit nor the CPL or the CRA/monitor will have access to the randomisation code.

The CRO will open the envelope containing the randomisation list only when data-entry is complete and decisions to be made in blinding, before data analysis, are final.

The CRO will notify breaking of the randomisation list to the Sponsor.

8.3.1 Emergency code and unblinding procedures

Unblinding of the code for specific subjects, if applicable, will be fully documented in the source documents and in the clinical study report.

8.3.2 Emergency individual envelopes

Inside the envelope, the randomisation code must be clearly indicated, reporting the allocated treatment.

The true randomisation code will be filed in the Investigator's study file in a sealed envelope for each subject, with the key for its identification. Copies of the emergency individual envelopes will be sent to the pharmacovigilance representative and to the Sponsor representative (if not coinciding).

Breaking of an individual randomisation code, by the Investigator during the study, is allowed only when knowledge of the code by the Investigator is essential for the subject's health. In these cases, the Investigator will open only the envelope related to the concerned subject. Individual code breaking will be clearly reported in the subject-related CRF and the envelope itself; the latter is sealed again.

In any case, the CRA/monitor must be informed within 24 h from code breaking.

The date and the reason for breaking the code must be recorded in the CRF and on the envelope. All envelope sets containing the randomisation code of each subject must be kept closed even after database lock. At the end of the study, all envelope sets will be sent to the Sponsor.

9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary variables

- Conjunctival anaesthesia evaluation by conjunctival pinching (with 0.3 mm forceps) at 5 min post-dose - only study eye (right eye).

9.1.2 Secondary variables

- Conjunctival anaesthesia evaluation by conjunctival pinching (with 0.3 mm forceps) at the pre-specified assessment time-points (see below) - only study eye (right eye)
- Ocular symptoms (burning, stinging, itching, foreign body sensation) using a 0-100 mm VAS- both eyes
- Visual acuity (EDTRS chart) – both eyes
- Objective ocular signs (Conjunctival redness, anterior chamber flare, conjunctival chemosis, eyelid swelling) by SLE- both eyes
- Corneal fluorescein staining by SLE- both eyes
- Intraocular pressure (IOP) - both eyes
- Fundus ophthalmoscopy (vitreous, macula, retina and optic nerve head) with the slit lamp- both eyes
- Treatment-emergent adverse events (TEAEs), assessed throughout the study
- Vital signs (blood pressure and heart rate).

9.2 Safety assessments

Safety and general tolerability of the investigational products will be based on TEAEs, ocular symptoms (0-100 mm VAS), physical examinations including body weight, vital signs, visual acuity, SLE, corneal fluorescein staining, fundus ophthalmoscopy and IOP results.

10 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated and compared using classic descriptive statistics, i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis of demographic, efficacy and safety data will be performed using SAS® version 9.3 (TS1M1) (12) or higher (the actual versions will be stated in the final report).

10.1 Analysis Sets

10.1.1 Definitions

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A subject will be defined as eligible if he/she meets all the inclusion/exclusion criteria. Otherwise he/she will be defined as a screen failure.

A subject will be defined as enrolled in the study if he/she is included in the interventional phase of the study. The enrolment will be performed through randomised allocation to a treatment arm.

An eligible but not enrolled subject will be defined as a reserve.

A subject will be defined as randomised in the study when he/she is assigned to a randomised treatment arm.

The following data sets will be used for the analysis:

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics
- Full Analysis Set (FAS): all randomised subjects, who receive the dose of the investigational product and have at least one post randomisation assessment of the primary efficacy data. This analysis set will be used for the primary efficacy analysis
- Per Protocol set (PP): all randomised subjects who fulfil the study protocol requirements in terms of investigational product intake and collection of primary efficacy data and with no major deviations that may affect study results. This analysis set will be used for sensitivity analyses
- Safety set: all subjects who receive at least one dose (drop) of the investigational product. This analysis set will be used for the safety analyses

Each subject will be coded by the CRO Biometry Unit as valid or not valid for the Enrolled set, FAS, PP set and Safety set. Subjects will be evaluated according to the treatment they actually receive (Enrolled set, FAS, PP set and Safety set).

10.1.2 Reasons for exclusion from the Full Analysis Set

Reasons for the exclusion of subjects from the Full Analysis Set are the following:

- failure to take the investigational product
- lack of any primary efficacy data post enrolment
- failure to satisfy major inclusion/exclusion criteria (eligibility deviations). Subjects who fail to satisfy an inclusion/exclusion criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:
  - the inclusion/exclusion criterion was measured prior to enrolment
  - the detection of the relevant eligibility deviations is completely objective
  - all subjects receive equal scrutiny for eligibility deviations (blind review)
  - all detected deviations of the particular inclusion/exclusion criterion are excluded

10.1.3 Reasons for exclusion from the Per Protocol set

Reasons for the exclusion of subjects from the Per Protocol set include (but are not limited to) the following:

- lack of compliance to the investigational product
- exposure to an investigational product different from the one assigned to the subject
- missing primary efficacy data
- failure to satisfy any inclusion/exclusion criteria (eligibility deviations)
- intake of prohibited medications

10.2 Sample size and power considerations

A total of 105 healthy men and women will be included in the study. Active vs. placebo treatment will have a 4:1 ratio.
Initially, local tolerability and safety will be evaluated on the first 20 enrolled subjects (16 treated with chloroprocaine 3% ocular gel and 4 with placebo).
After the first 20 subjects have completed the study, local tolerability and safety data will be evaluated and if treatment safety is confirmed, efficacy, beside local tolerability and safety, will be assessed on the 85 subsequent subjects (68 active gel and 17 with placebo).

Sample size for the efficacy evaluation was formally calculated as follows:
Sample size per group was calculated by comparing two independent proportions (experimental and placebo success rate) with a two-sided alpha=0.05 and a power of 0.95. This is based on the assumption, that the experimental success rate is 80% and the vehicle success rate is 30%, taking a dropout rate of 20% into account. For sample size estimation, NQuery (Version 4.0) was used implementing formulas described in Chow et al (2008) (13).

10.3 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics.

10.4 Analysis of efficacy parameters

10.4.1 Primary end-point

Primary end-point is defined as the proportion of subjects gaining full anesthesia of the ocular surface 5 minutes after administration of the investigational product for the 2 treatment arms (cornea pinching assessment).

The result of the anesthesia will be coded as success/failure, listed by subject and summarized overall and by treatment group using contingency tables. Resulting proportions will be presented together with 95% confidence interval. The 2 groups (active and placebo) will be compared using Pearson's χ^2 test. The null hypothesis of equal success between the 2 treatment arms at the α=0.05 level will be rejected if:

$$\left| \frac{\widehat{p_1} - \widehat{p_2}}{\sqrt{\frac{\widehat{p_1}(1-\widehat{p_1})}{n_1} + \frac{\widehat{p_2}(1-\widehat{p_2})}{n_2}}} \right| > Z_{\alpha/2}$$

where p_1 is the proportion of subjects who meet the primary endpoint in the active group, while p_2 is the proportion of subjects who meet the primary endpoint in the vehicle (placebo) group.

10.4.2 Secondary end-points

Time to anesthesia and duration of anesthesia will be listed and summarized overall and by group using descriptive statistics (mean, median, standard deviation, minimum, maximum, 95% confidence interval on the mean, and number of observations). The 2 groups (active and placebo) will be compared using non-parametric Mann-Whitney's test for continuous variables.

10.5 Safety and tolerability evaluation

10.5.1 Adverse events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of investigational product and not worsening after the first dose of investigational product
- TEAEs: all AEs occurring or worsening after the first dose of investigational product

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness (if applicable), relationship to treatment and severity.

10.5.2 Physical examination

Date of the physical examination, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. Body weight values will be listed and summarised by descriptive statistics.

10.5.3 Ocular symptoms

VAS scores for ocular tolerability parameters (burning, stinging, itching, foreign body sensation) and their changes from baseline will be listed and summarised by treatment and eye using descriptive statistics (mean, SD, CV%, minimum, median and maximum).

Changes from baseline will be evaluated and compared between treatments.

10.5.4 Visual acuity

Visual acuity results will be listed by subject and summarised for each eye by descriptive statistics.

10.5.5 Slit lamp examination, corneal fluorescein staining and fundus ophthalmoscopy results

Scores or values for Slit lamp examination (SLE) parameters, Fundus ophthalmoscopy parameters and Corneal fluorescein staining parameters and their changes from baseline will be listed and summarised for each eye using descriptive statistics (mean, SD, CV%, minimum, median and maximum).

10.5.6 Intraocular pressure

IOP values will be listed and summarised for each eye by descriptive statistics.

10.5.7 Vital signs

Vital signs values will be listed and summarised by descriptive statistics.

11 DEFINITION AND HANDLING OF AEs AND SAEs

11.1 Applicable SOPs

AEs definition, classification and management will follow the SOP of CROSS Research S.A., based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical centres.

A brief summary of AE definition, classification and management is reported below.

11.2 Definitions

- **Adverse event (AE)**

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

- **Adverse Drug Reaction (ADR)**

Any noxious and unintended response to a medicinal product (i.e. a causal relationship between a medicinal product and an AE is at least reasonably possible in the Investigator's or Sponsor's opinion, the relationship cannot be ruled out) resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

- **Pre-treatment AE (PTAE)**

Any AE occurring before the first dose of a medicinal product and not worsening after the first dose. The following medical occurrences and clinical investigations are the only clinically significant events which, according to the Investigator judgement, can be defined and recorded as PTAEs:

- trauma (fractures, sprains, strains, falls, domestic accidents, car accidents, etc.) occurred after the signature of the informed consent and before the first medicinal product administration
- new measurements (vital signs, laboratory parameters, etc.), performed after the signature of the informed consent and before the first medicinal product administration, which show a clinically significant worsening in comparison with a previous (baseline) measurement performed after the signature of the informed consent
- any disease diagnosed after the anamnesis recorded at visit 1 and before the first medicinal product administration
- physical and mental status changes (pre-syncope, anxiety, dizziness, fainting, etc.) occurred after the signature of the informed consent and before the first medicinal product administration

- **Treatment-emergent AE (TEAE)**

Any AE occurring or worsening after the first dose of a medicinal product

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event that may jeopardize the subject's health status or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are cancer, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse

- **Unexpected ADR**: an ADR the nature or severity of which is not consistent with the Reference Safety Information (RSI)

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, Chloroprocaine Investigator's Brochure (IB) will be used.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

An ADR that is both unexpected (not consistent with the RSI) and also meets the definition of a SAE.

11.3 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: last follow-up visit/ETV

An AE occurring after the last follow-up visit/ETV and coming to knowledge of the Investigator (e.g. by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the Investigator's judgment.

11.4 AEs recording

All AEs derived by spontaneous, unsolicited reports of the subjects, by observation and by routine open questioning should be collected and reported.
The following minimal information will be recorded for an AE (detailed explanation for each element is available in the SOP or in the operative summary made available to the clinical centre) in the source documents and later transcribed into the CRF:

1. Adverse Event: progressive number of the adverse event

2. Description: verbatim description of the adverse event or
Follow-up: progressive number of follow-up of the adverse event

3. Acknowledgment Date/Time: acknowledgment date/time of the adverse event or
Follow-up Date/Time: follow-up date/time of the adverse event

4. Start Date/Time: start date/time of the adverse event

5. End Date/Time: end date/time of the adverse event

6. Affected Body Area: anatomical location relevant for the event

7. Whether the adverse event start before or after the first intake of the study drug or whether the adverse event has worsened or not after the first intake of the study drug

8. Last Study Drug Administration Date/Time Before Onset: if the adverse event started after the first administration of the study drug, the date/time of last administration of the study drug before the onset of the adverse event or
Last Study Drug Administration Date/Time Before Worsening: In case of treatment emergent adverse event, the date/time of the last administration of the study drug(s) before the worsening of the adverse event.

9. Investigator's opinion about the reasonable possibility of a causal relationship with the study drug.

10. Investigator's opinion about other causal relationship (e.g. non study drug, concomitant therapy, study device, etc.).

11. Severity: the severity or intensity of the event

- 1 Mild
- 2 Moderate
- 3 Severe

12. Pattern: Used to indicate the pattern of the event over time

- 1 Single Event
- 2 Continuous
- 3 Intermittent

13. Serious Adverse Event

14. Action Taken with Study Drug: describes changes to the study drug as a result of the event. It is specifically for actions taken with the study drug

- 1 Dose Not Changed
- 2 Dose Increased
- 3 Dose Reduced
- 4 Drug Interrupted (i.e. temporary stop)
- 5 Drug Withdrawn (i.e. definitive stop)
- 6 Not Applicable (e.g. drug administration not started yet or completed)
- 7 Unknown

15. Concomitant Therapy: if a concomitant therapy is given, it must be reported in the specific CRF forms

16. Study Discontinuation: if the adverse event cause the subject to be discontinued from the study

17. Other Action Taken: other actions taken as a result of the event that are unrelated to dose adjustments of study drug

18. Outcome: Outcome of the event

- 1 Recovered/Resolved
- 2 Recovered/Resolved With Sequelae
- 3 Recovering/Resolving
- 4 Not Recovered/Not Resolved
- 5 Fatal
- 6 Unknown

11.5 SAEs reporting

IMPORTANT: National regulations and requirements for SAE reporting **prevail**, however, in general, the following indications should be followed.

The Investigator must report to the Sponsor any SAE within 24 h of becoming aware of the event. The Investigator, within the same timeframe, should also inform the study monitor and the CRO. The Investigator shall notify the competent Ethics Committee (EC) within 7 days of any SAE with lethal outcome occurred during a study. If the Investigator is initially unable to obtain all the necessary details for completing the form, he/she should in any case transmit all the available information. The Investigator should provide an appropriate follow-up of SAEs to all concerned parties.
Seriousness and causality must be assessed by the Investigator. Expectedness is usually assessed by the Sponsor.
If the Investigator is unable to assess the causality it is recommended to adopt a conservative approach and treat the event as a suspected adverse reaction until follow-up information is available.
The Sponsor may also make an assessment of causality, independent of that of the Investigator. The most conservative approach should be taken when it comes to regulatory reporting. Under no circumstances should the Sponsor downgrade the Investigator's opinion or put the Investigator under pressure to change his/her assessment. In case of disagreement, both the opinion of the Investigator and the Sponsor should be provided in the report.
The Sponsor will evaluate the SAE expectedness on the basis of the RSI.

11.6 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the Sponsor (day 0).
For fatal and life-threatening SUSARs the EC and Competent Authority (CA) should be informed as soon as possible and in any case within 7 days.

If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

- Valid EudraCT number (where applicable)
- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect investigational product (including active substance name, code)
- A causality assessment (a reasonable possibility of a causal relationship with the study drug can be excluded only if there is information supporting this decision, otherwise it cannot be excluded).

11.7 Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting when they might materially alter the current benefit-risk assessment of a medicinal product or would be sufficient to consider changes in the medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g.: a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical trial and are reported to the Investigator by the subject.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the subjects, such as :
  - a SAE which could be associated with the trial procedures and which could modify the conduct of the trial
  - a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical trials.

11.8 SAEs: contacts

SAEs must be reported on SAE reporting forms and faxed/emailed within 24 H to Corporate Drug Safety Unit of the sponsor - contact details below:

Fax: +41(0)91.646.85.61
Phone: +41(0)91.640.42.50
Email: corporate_drug_safety@sintetica.com

12 DATA MANAGEMENT PROCEDURES

12.1 Data collection – CRFs

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRFs. He must also check that the data reported in the CRFs correspond to those in the subject's source documents.
To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the Investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialled. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The Investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the Investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the Sponsor.

12.2 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the Sponsor study code (i.e. CHL.3-01-2020), the 3-digit site number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (e.g. 001, 002, etc.). Study code, site number, screening number and subject randomisation number are separated by slashes ("/"). The last 8 digits of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject randomisation numbers separated by a slash, or the last 4 digits of the unique subject identifier (not enrolled subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report.

12.3 Database management

The CRO will provide a double data entry with 100% sight verification of data and discrepancy resolution by a second data entrist and will update and verify the database and create the final SAS data sets. The final data file will be transferred to the Sponsor in the agreed format with all the other study documentation.

12.3.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).
Previous and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE). The version of the coding dictionaries will be stated in the study report.

13 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The monitoring visits will be conducted by Clinical Medical Services of Maria Pia Savorelli and the Sponsor (see § 16.3).

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements.

Adequate time and availability for monitoring activities should be ensured by the Investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the Investigator will assure support to the monitor at all times.

The Investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the Sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP guidelines.

13.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System that includes quality controls and audits at different study steps with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOAC principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

The CROs and the Sponsor will be responsible for their respective activities.

The Sponsor may transfer any or all of the Sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the Sponsor.

13.3 Applicable SOPs

The Sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for review, if required.

13.4 Data access

The Investigator and the CRO will ensure that all raw data records, medical records, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IEC review, and regulatory inspections.

13.5 Audits and inspections

The Sponsors, independent bodies acting on behalf of the Sponsor and the CRO have the right to perform audits according to ICH-GCP responsibilities.

The study may also be inspected by regulatory authorities.

The Investigators and the CROs agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorised individuals to have access to all the study documentation.

14 ETHICAL CONSIDERATIONS

14.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.
The approval of the study protocol by the local (Canton Ticino) IEC and by the Federal Health Authorities (Swissmedic) will be obtained before the start of the study.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirements.

14.2 Informed consent

Before being enrolled in the clinical study, the subjects must have expressed their consent to participate, after the Investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and regulatory authorities. It will include all the elements required by law according to the ICH-GCP recommendations.
In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment (information on the investigational product(s) and treatment procedures, as applicable)
- any potential negative effects attributable to the study product or treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The Investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the Investigator and the subject.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the Investigator's study file according to the regulatory requirements (see § 15.3).
The Investigator will allow inspection of the forms by authorised representatives of the Sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.
A blank copy of the information sheet and the informed consent form is appended to this protocol.

14.3 Insurance policy

An insurance cover has been issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

14.4 Withdrawal of subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

14.4.1 Primary reasons for discontinuation

- **Adverse event**: Any (significant) adverse event that in the opinion of the Investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 11.2.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by Sponsor**: an indication that a clinical study was stopped by its Sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

14.4.2 Discontinuation procedures

For any subject discontinuing the study, the Investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)
- arrange for alternative medical care of the withdrawn subject, if necessary
- record the subject decision about the use of collected biological samples
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation

- record in the CRF any follow-up, if the subject is withdrawn for an AE

Subjects withdrawn from the study will retain their randomisation number and will not be replaced.

14.5 Study termination

The study will be considered terminated at the date of the last visit of the last subject or upon completion of any follow-up procedure described in protocol. The Investigator and the Sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately and immediately reported to Swissmedic and EC (i.e. within 15 days).

15 ADMINISTRATIVE PROCEDURES

15.1 Material supplied to the clinical centre

Beside the investigational products, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- CRF for each subject plus some spare copies
- copy of the Investigator's Brochure (IB)
- informed consent forms

Moreover, before the start of the study, the Investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, Investigator and study staff list form.

15.2 Protocol amendments

In order to obtain interpretable results, neither the Investigator nor the Sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between the Investigator and the Sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All substantial amendments will be sent to EC and Swissmedic, as appropriate. The amendment will be applicable only when it is approved, unless the changes consist of urgent safety measures to protect study subjects.

Non substantial amendments will be notified according to the current regulations.

15.3 Study documentation and record keeping

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

The Investigator must keep source documents for each subject in the study. All information on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information and the original signed informed consent forms.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The Investigator and the Sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects, insurance contracts, certificate of analysis of the investigational products, drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the Investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The Investigator and the Sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the Investigator and the Sponsor as long as needed to comply with ICH-GCP, national and international regulations. By signing the protocol, the Investigator and the Sponsor agree to adhere to these requirements.

15.4 Study subjects' recruitment

Study participants will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enrol subjects in a new study. Before the start of the new study, the principal Investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential participants to propose the study and evaluate their interest and availability. In addition to the volunteers' database, new subjects often call or email the CRO asking to become a research volunteer, after being informed of the clinical site activities from other volunteers or friends or after checking the company web site.

The CRO and its clinical site have detailed SOPs on the recruitment process.

15.5 Confidentiality and data protection

By signing this protocol, the Investigator and the CRO agree to keep all the information provided by the Sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the Sponsor (protocols, IB, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the Sponsor to the Investigator and to the CRO cannot be disclosed to others without direct written authorisation from the Sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected in the CRFs during the study will be documented in an anonymous way (see § 12.2). If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the monitor, the Sponsor and the Investigator will be bound to keep this information confidential.

15.6 Publication policy

The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.
Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

As the Sponsor agrees that the study results can be published by the Investigator, the Investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the Sponsor before any public disclosure.
This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The Sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).

The Investigator will also be provided by the Sponsor with the clinical study report and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).
On an exceptional basis, the Sponsor may temporarily delay registration of certain data elements (e.g. compound, name, outcome, measures, etc.) to seek necessary intellectual property protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

According to The Federal Act on Research involving Human Beings and the Ordinance on Clinical Trials in Human Research, the study will be registered and published in a WHO primary register or clinicaltrials.gov as well as in the supplementary federal database.

16 STUDY RESPONSIBLE PERSONS

16.1 Sponsor

Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland
Phone: +41.91.640.42.50
Fax: +41.91.646.85.61

Sponsor representatives
Corporate Director Scientific Affairs
Elisabetta Donati
Email: edonati@sintetica.com

Clinical Project Leader
Erika Botti
Email: ebotti@sintetica.com

Medical Expert
Claudio Camponovo, MD
Department of Anaesthesiology, Clinica Ars Medica,
Via Cantonale, CH-6929 Gravesano, Switzerland
Phone: +41.91.611.6211
Fax: +41.91.605.1559
Email: ccamponovo@arsmedica.ch

16.2 Institutes performing the study

16.2.1 Clinical centre

CROSS Research S.A. – Phase I Unit, Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.64.04.450
Fax: +41.91.64.04.451
Email: clinic@croalliance.com

Principal Investigator
Milko Radicioni, MD

16.2.2 Ophthalmological assessments

Ophthalmologists
Elena Gibin, MD
gibin@centromedico.ch

Matteo Ghidoni
ghidoni@centromedico.ch

PDS Medical SA, Via Vela 42, 6834 Morbio Inferiore, Switzerland
Phone: +41 91 683 07 40

Fax: +41 91 683 07 41

16.3 Co-ordination, monitoring, data analysis & reporting

CROSS Research S.A., Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.6300510
Fax: +41.91.6300511

Coordination
Chiara Castiglioni, Clinical Project Leader and Senior CRA
Email: projectmanagement@croalliance.com

Medical Writing Representative
Chiara Leuratti, Clinical Projects Unit Head
Email: medicalwriting@croalliance.com

Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head
Email: statistics@croalliance.com

Quality Assurance Unit Representative
Mario Corrado, Quality Assurance Manager, Unit Head
Email: qau@croalliance.com

16.4 Monitoring

Clinical Medical Services di Maria Pia Savorelli, Via Indipendenza 29/A, CH-6883 Novazzano, Switzerland
Mobile: +41 79 827 27 67
Email: cmed@cmed.ch

17 REFERENCES

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