Clinical Study Protocol Nº: CHL.3/01-2019/M

A prospective, observer-masked, randomized clinical trial to investigate and compare the clinical efficacy of chloroprocaine 3% gel and tetracaine 0.5% eye drop as topical anestheticsin phacoemulsification.

EudraCTNumber: 2019-001660-30

Test product:	Chloroprocaine3% ophthalmicgel, Sintetica S.A., Switzerland
Reference product:	Tetracaine 0.5% ophthalmic solution
Sponsor:	Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland Phone: +41.91.640.42.50; Fax: +41.91.646.85.61
Development phase:	Phase III
Version and date:	Version 2.0May12, 2020

This study will be conducted in accordance with Good Clinical Practice (GCP), ICH topic E6 (R2), applicable regulatory requirements and data protection law

Amendments	
No.	Date

PROTOCOL APPROVAL

SPONSOR
Sintetica S.A., Switzerland

Clinical Project Leader
ElisabettaDonati, CorporateDirector Scientific Affairs

15/May/2020 — Date

Signature

INTERNATIONAL STUDY COORDINATOR
Professor JorgeAlio

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.

May 15 2020 — Date

Signature

BIOSTATISTICIAN
AlexandrosGryparis

First Name, Last Name

May 14th, 2020 — Date

Alexandros Gr-lparis — Signature

INVESTIGATOR SIGNATURE PAGE

The signature below:

- Confirms my agreement to conduct the trial in compliance with Good Clinical Practices (GCP), applicable regulatory, including General Data Protection Regulation, and the clinical study protocol requirement(s),
- Confirms my agreement to comply with procedures for data recording/reporting,
- Confirms my agreement to permit monitoring, auditing, and regulatory inspection,
- Confirms my agreement to retain the study essential documents in the Investigator files until Sponsor informs me these documents are no longer needed (e.g. over 15 years),
- Ensure that all persons assisting with the study are adequately informed about protocol, the investigational product(s) and their trial-related duties and functions,
- Confirms that I have read this protocol and I agree to comply with all parts or items.

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

TRIAL SITE

Principal Investigator

_____	_____	_____
First Name –Last Name	*date*	*signature*

Contacts page for the study

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STUDY SYNOPSIS

StudyTitle	A prospective, observer-masked, randomized clinical trial to investigate and compare the clinical efficacy of chloroprocaine 3% gel and tetracaine 0.5% eye drop as topical anestheticsin phacoemulsification
Sponsor	Sintetica S.A.
Protocol Sponsor code	CHL.3/01-2019/M
EudraCT-Number	2019-001660-30
Clinical phase	Phase III
Study design	Multicenter, international, randomized, competitive Phase III pivotal equivalence study
Planned Schedule	Planned initiation: Q2 2020 Planned Last Patient Last Visit (LPLV): September 2020
Planned n. of centers / countries	Approximately 30centers / 3-4 European countries
Indication	Local anesthesia by topical instillation
Test Product	Chloroprocaine 3% gel
Referenceproduct	Tetracaine 0.5% eye drops
Randomization	Patients will be allocated to the Test (Chloroprocaine) arm or Reference (tetracaine) arm according to a 1:1 ratio
Sample Size	Approximately 342 male/female outpatients, aged ≥ 18 years, scheduled to undergo cataract surgery in a single eye at a time
Study Duration	Up to 17weeks duration per subject Screening: D-90 to D-1 Randomization: D1 Follow-up: D2(on-site visit or phone contact according to site usual practice), Final visit: D8, Optional visit: D28 (phone contact in case of Adverse Event at D8)
Inclusion criteria	To be enrolledin this study, subjects must fulfil all these inclusion criteria: *1.* Signed and datedinformed consent *2.* Male or femaleaged≥ 18 years *3.* Senile or pre-senilecataract *4.* Scheduled to undergo cataract surgery in a single eyeat a time (clear corneal self-sealing incisions - phacoemulsification – foldable intra-ocular lens surgery with injector)
Exclusion criteria	Patients fulfilling at the selection visit ONE OR MORE of the following exclusion criteria will not be enrolled in the study: ***Ophthalmic exclusion criteria*** ➢ Surgical conditions in the eye to be operated: *1.* Combined surgery *2.* Previous intraocular surgery *3.* Previous corneal refractive surgeries less than 6 months before screening ➢ Non-surgical conditions in the eye to be operated: *4.* Non Senile or non pre-senilecataract (e.g.: traumatic, pathological or congenital cataract) *5.* Pupillary abnormalities (irregular, etc.) *6.* Iris synechiae *7.* Eye movement disorder (nystagmus, etc.) *8.* Dacryocystitis and all other pathologies of tears drainage system *9.* History of Inflammatory ocular disease (Iritis, uveitis, herpetic keratitis) *10.* Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration and superficial punctuate keratitis) *11.* History of ocular traumatism, infection or inflammation within the last 3 months

12. Pseudo-exfoliation, exfoliative syndrome
13. Prior intravitreal injections within 7 days of the surgery
14. IOP over 25mmHg under treatment

- Ophthalmic conditions in the contra-lateral eye:
  15. Best corrected visual acuity < 1/10
  16. Patient already included in the study for phakoexeresis
  17. History of ophthalmic surgical complication (cystoid macular oedema, etc.)

Systemic/non ophthalmicexclusioncriteria

- General history:
  18. Diabetesmellitus
  19. Surdity
  20. Pakinsondisease
  21. Excessive anxiety
  22. Any other medical or surgical history, disorder or disease such as acute or chronic severe organic disease: hepatic, endocrine neoplasic, hematological diseases, severe psychiatric illness, relevant cardiovascular abnormalities (such as unstable angina, bradycardia, atrial fibrillation,uncontrolled hypertension: systolic blood pressure over 140 mm Hg, diastolic blood pressure over 90 mmHg) and/or any complicating factor or structural abnormality judged by the investigator to be incompatible with the study.
- Allergic history:
  23. Known hypersensitivity to sulfonamides products or any of the components of the study medications or to test products

Specific exclusion criteria for women

24. Pregnancy (positive pregnancy test), lactation
25. Women of childbearing potential without an acceptable effective method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant) until end of the study participation

OR

26. Women not hysterectomized, not menopaused nor surgically sterilized.

Exclusion criteria related to general conditions

27. Inability of patient and/or relatives to understand the study procedures and thus inability to give informed consent
28. Non-compliant patient and/or relatives (e.g. not willing to attend the follow-up visits, way of life interfering with compliance)
29. Participation in anotherclinicalstudy
30. Already included once in this study
31. Ward of court
32. Patient not covered by the Social Security

Exclusion criteria related to previous and concomitant medications / non-product therapies

Patient using any of the following previous and concomitant medication / treatment (according to the described periods) will not be included in the study:

NOT ALLOWED CONCOMITANT MEDICATIONS				
Before the surgery			**Surgery**	**After surgery**
30 days	15 days	7 days	Day 1	Day 2 to Day 28
Any change in concomitant anti-depressant medication ……				
	Systemic opioids and morphinic drugs			
	Topical ocular treatment with anaesthetic action*……..…			
		Prior intravitreal injections ……..		

		Sulfonamides products,, Others systemic antalgics drugs *(except paracetamol)*..............
		Any change in other systemic medication already ongoing before selection visit
	**except the pre-, peri-operative and post-operative therapeutics procedure to be followed according to the protocol.*	
Primary objective	Equivalence evaluation of Test versus Reference products in terms of proportion of subjects with a successful surface anesthesia for cataract surgery, without any supplementation (see definitions below) at T4(just before Intra Ocular Lens implantation) <u>*Successful surface anesthesia*</u>: The patient assessment of ocular discomfort during surgery must be 0 (=No pain or discomfort) or 1 (=Occasional pressure sensation, less than 5 separated times during procedure) without any supplementation at T4. <u>*Supplementation*</u>*:*Intra-operative analgesia, including additional LA drops administration,after the beginning of the surgery.	
Secondary objective	Assess the clinical efficacy and safety of 3% chloroprocaine gel compared to those of tetracaine 0.5% eye drop.	
Primaryendpoint	The proportion of subjects in each treatment group with a successful surface anesthesia, without any supplementation at the time point T4. A successful surface anesthesia is equal to 1 and is defined as ocular discomfort equal to 0 (=no pain or pressure) or 1 (=occasional pressure sensation, less than 5 separated times during procedure).It is equal to 0 otherwise (e.g. ocular discomfort > 1).	
Secondaryendpoints	*Efficacy end-points during surgery:* ➢ Successful surface anesthesia at T1, T2and T3 based on patient questioning: Patient's operated eye discomfort. ➢ Time to obtain sufficient anesthesia (use of forceps). ➢ Total time of anesthesia ➢ Blinking reflex dropping a water drop at the end of the surgery ➢ Number of supplemental drops necessary for obtaining and/or maintaining anesthesia ➢ Supplementary treatments (general anesthesia or intra-operative systemic analgesia) necessary for obtaining and/or maintaining anesthesia ➢ Total surgical time ➢ Assessment of surgical comfort by the surgeon of each stage of the surgical procedure. ➢ Assessment of the global efficacy by the surgeon for anesthesia.	
Secondaryendpoints	*Safety end-points:* - *Ocular symptoms* (pain, irritation/burning/stinging, photophobia, foreign body sensation) will be graded by the patients according to the following scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. - *Objective ocular signs* (palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, follico-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells) assessed by slit lamp examination, flare, and other objective ocular signs will be graded according to the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Modification of the basal status of the following assessments: - *Slit lamp examination and fluorescein test* - *Endothelial cell counts* (specular microscopy) - *Corneal thickness* (pachymetry) - *Best far corrected visual acuity* - *Fundoscopy* - *Intra-ocular pressure* - *Vital signs* (blood pressure and heart rate)	

	- *AEs occurrence* - *Surgeon satisfaction*: "How do you consider the study product global tolerance" will be graded according to the following scale: 0 = very satisfactory, 1 = satisfactory, 2 = not very satisfactory, 3 = unsatisfactory. - *Patient global satisfaction at Visit 3/D2* (5-scale pointsquestionaireread by a masked observer).
Study Procedures	The study will include a Selection visit (Day -90/Day -1), an Inclusion visit (Day 1/surgery day), a Follow-up visit (Day 2, phone visit), a Final visit (Day 8), and a Follow-up phone call - Optional (Day 28, phone visit). **Selection visit (Visit 1, Day -90/Day -1)** Patients scheduled to undergo cataract surgery in a single eye will be informed about the aims, procedures and possible risks of the study and will be asked to sign the informed consent form for the inclusion in the trial. Patients will be assigned a screening number. Routine pre-surgery assessments will be performed according to the hospitals' standard procedures, and the study inclusion/exclusion criteria will be verified. Protocol specific assessments will be performed according to table 1 (see table 1- study schedule). **Inclusion visit/Surgery (Visit 2, Day 1)** Before the anesthesia, patients will be questioned about previous and concomitant ocular and non-ocular treatments. Inclusion /exclusion criteria and patient status will be verified. Blood pressure, heart rate, AEs occurrence will be assessed. Patients will be randomized to either chloroprocaine 3% gel (Test) or tetracaine 0.5% eye drop (Reference) treatment group. Patient discomfort in the operated eye will be assessed(see table 1- study schedule). **Follow-up visit/phone visit (Visit 3, Day 2)** Concomitant ocular and non-ocular treatments, AEs, and patient global satisfaction will be assessed (see table 1- study schedule). **Final visitvisit (Visit 4, Day 8 ± 1 day)** Concomitant ocular and non-ocular treatments, ocular symptoms, best far corrected visual acuity in both eyes, endothelial cell count, corneal thickness, blood pressure and heart rate, and AEs will be assessed. Slit lamp examination and fluorescein test, IOP in both eyes, and fundoscopy will be performed. In case an AE is not resolved at vist 4 Day 8, a final follow-up phone contact will be performed at D28(see table 1- study schedule). **Optional visit/phone visit (Visit 5, Day 28 ± 3 days)** Concomitant ocular and non-ocular treatments and AEs resolution will be assessed(see table 1- study schedule).
Definition of analysis sets	1. *Safety Set*: the safety set is defined as all the patients enrolled in the study for whom there is evidence that they used study medication and for whom any follow-up information is available. 2. *Full Analysis Set (FAS)*: the FAS will include all the patients enrolled in the study for whom any follow-up efficacy information is available. 3. *Per Protocol Set (PPS)*: the PP set will include all the patients of the FAS who did not show any major protocol violation. The statistical analysis of the onset data and of efficacy will be performed on the basis of the FAS and the PPS. The primary population for the assessment of efficacy will be the PPS, while the statistical analysis on the FAS population will be considered as sensitivity analysis. The analysis of safety will be performed on the basis of the safety set.
Statisticalanalysis	Data documented in this study and the parameters measured will be evaluated and presented using descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values for quantitative variables, and absolute and relative (%) frequencies for qualitative variables. The statistics will be reported by treatment group. For the

	variables recorded for both eyes, the statistics will be reported by treatment group, separately for the eye to be operated and for the other eye. Confidence intervals will be reported, where appropriate. If not stated elsewhere, these intervals will be two sided in each case and provide 95% confidence. Efficacy will be evaluated in the operated eye using mixed effects models (adjusting for center and country using random effects). The primary endpoint of the study is defined as the proportion of subjects in each treatment group with a successful surface anesthesia, without any supplementation at the time point T4. A successful surface anesthesia (=1) is defined as ocular discomfort equal to 0 (=no pain or pressure) or 1 (=occasional pressure sensation, less than 5 separated times during procedure), and it is equal to 0 otherwise. A statistical analysis plan (SAP) will be provided before database closure. The statistical analysis will be performed using RStudio v. 1.2.5001 and/or IBM SPSS Statistics v. 25 (or newer) for Windows.

TABLE 1. - STUDY SCHEDULE

Study procedure	**Visit 1 Selection visit D-90/D-1** ***By Masked-observer***	**Visit 2 Inclusion Visit Surgery D1** ***By Surgeon***	**Visit 3 Follow-up visit D2 (phone visit)** ***By Masked-observer***	**Visit 4 Final visit D8 (+/- 1 day)** ***By Masked-observer***	**Visit 5[3] Optional visit D 28 (+/- 3 days)phone visit** ***By Masked-observer***
Informed consent	X				
Demography	X				
Ocular medical and surgical history	X				
Systemic medical and surgical history	X				
Urine pregnancy test	X	X[4]			
Previous and concomitant ocular and non-ocular treatments	X	X	X	X	X
Assessment of patient's discomfort		X[1] [2]			
Ocular symptoms	X			X	
Best far corrected visual acuity in study eye	X			X	
Slit lamp examination and fluorescein test	X			X	
IOP in botheyes	X			X	
Assessment of surgical performance		X			
Funduscopy	X			X	
Endothelial cells count by specular microscopy	X			X	
Corneal thickness by pachymetry	X			X	
Retinal thickness by Optical Coherence Tomography	X				
Cardiovascular parameter (blood pressure and heart rate)	X	X[2]		X	
Adverse events		X	X	X	X
Verification of inclusion and exclusion criteria / Status of the patient	X	X			
Allocated treatment group		X			

Study procedure	**Visit 1 Selection visit D-90/D-1** ***By Masked-observer***	**Visit 2 Inclusion Visit Surgery D1** ***By Surgeon***	**Visit 3 Follow-up visit D2 (phone visit)** ***By Masked-observer***	**Visit 4 Final visit D8 (+/- 1 day)** ***By Masked-observer***	**Visit 5(3) Optional visit D 28 (+/- 3 days)phone visit** ***By Masked-observer***
Dose regimen compliance		X			
Patient global satisfaction (questionnaire read by a masked observer)			X		
Surgeon global satisfaction		X			

(1) -T1:just before first incision
-T2:end of capsulorehexis
-T3:end of phacoemulsification
-T4:just before intra ocular lens implantation

(2) By masked-observer

(3) Visit 5 must be conducted only in case of AE at Visit 4

(4) only if Visit 2 more than 30 days after visit 1

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable-Legible-Contemporaneous-Original-Accurate
ANOVA	Analysis of Variance
BP	Blood Pressure
BSS	Balanced Salt Solution
CA	CompetentAuthority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CRO	ContractResearchOrganization
CSP	ClinicalStudy Protocol
CRS	ClinicalStudy Report
CV	Coefficient of Variation
D	Day
DBP	Diastolic Blood Pressure
EC	EthicsCommittee
ETV	EarlyTerminationVisit
FAS	Full Analysis Set
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hg	Mercury
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IOL	Intra Ocular Lens
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	InvestigationalMedicinal Product
IV	Intravenous
LSLV	Last Subject Last Visit
LA	Local Anaesthesia
MAR	MissingatRandom
MedDRA	Medical Dictionary for Regulatory Activities
MF	Missing as Failure
MI	Multiple Imputation
NA	NotApplicable
NSAIDs	Non-Steroidal Anti-InflammatoryDrugs
PK	Pharmacokinetics
PNB	Peripheal Nerve Block
PP	Per Protocol
PT	PreferredTerm
PTAE	Pre-TreatmentAdverse Event
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
T	Time
WC	Worst Case
WHODDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

Cataract surgery has become one of the most prevalent surgical procedures due to changes in population structure and increased life expectancy. Continually improving surgical techniques require less extensive anesthesia and decrease the need for hospitalization and postoperative controls.
Topical local anaesthetics (LAs) play an important role in the practice of ophthalmology, especially for less invasive outpatient surgeries, including cataract surgery.
Cataract surgery consists of the replacement of the natural lens of the eye that has become cloudy with a new and transparent intraocular lens.
Several improvements have been implemented in the past for this type of surgery. The eye incision decreased from 12 mm to 2.2 mm with the development of phacoemulsification and foldable intraocular lenses that are injected into the eye through special delivery systems.
The procedure is bloodless, because conjunctival incisions are no longer performed. The procedure lasts only 10–15 minutes in uncomplicated cases, with a very high success rate and is performed on an outpatient basis. Intraoperative and postoperative complications are very low.
As a result, the retrobulbar or peribulbar needle anaesthesia that had been used for more than a century was almost entirely abandoned about 15 years ago in favour of a new type of anaesthesia, which only requires application of anaesthetic drops (5). Topical anaesthesia has been adopted in cataract surgery because there is no blood in cut or touched tissues that could remove the anaesthetic drug, eyeball akinesia is no longer required, the procedure is usually short, additional anaesthesia by either drop or needle can be applied at any time, and there is no risk of globe perforation by needles.
Anaesthetics topically applied to the eye act directly on the corneal epithelium and stroma, and the portion of drug penetrating into the anterior chamber suppresses pain arising from the iris and ciliary body. The duration of effect of topically applied anaesthetics depends on the properties of the drug used. Usually it lasts up to 15–20 minutes for the commonly used agents, but eye drop instillation can be repeated at intervals during surgery if needed.
Current practices for ocular topical anaesthesia in Europe include topical liquid oxybuprocaine, tetracaine and lidocaine. It has been theorized, and recent studies support the idea, that gel formulations of local anesthetic may enhance anaesthetic effect, and therefore be superior to anaesthetic solutions for topical cataract surgery.

1.2 Rationale

1.2.1 Nonclinical background information

Animal studies conducted by the intended route of administration demonstrated that chloroprocaine 3% hydrochloride eye gel is efficacious and locally well tolerated. In none of these studies, systemic signs of toxicity were recorded at clinical observation.
Furthermore, repeat-dose toxicity studies performed in rats and dogs by the intrathecal route did not reveal any macroscopic or microscopic finding in any organ.
Taking into consideration that chloroprocaine is a local anaesthetic which is intended for a “one-shot” administration, there are acute toxicity studies performed by intraperitoneal route in mice and intravenous route in guinea pigs and dogs which can be useful to roughly estimate safety margins, with respect to the maximum recommended human dose for chloroprocaine hydrochloride 3% eye gel.

1.2.2 Clinical background information

There is a long history of use of chloroprocaine and the amino ester class of anaesthetics in USA, Canada and Switzerland. In particular, chloroprocaine has been FDA-approved since 1955 and is currently marketed in the US and Canada as Nesacaine® (1% and 2%), Nesacaine®-MPF (2% and 3%), both sponsored by Fresenius Kabi for infiltration, nerve block (up to 800 mg) and epidural block and in US as Sintetica's Clorotekal® 1% for intrathecal injection since 2017.
In Europe, Sintetica's Ampres® 1% is approved for intrathecal administration. Since July 2015, it is present on the Swiss market for local anaesthesia by infiltration, for Peripheral Nerve Block (PNB) and for epidural block, respectively.
Thanks to very favourable PK characteristics, chloroprocaine is currently considered the local anaesthetic with the safest toxicological profile, and Sintetica already performed 3 different clinical trials testing the efficacy and safety of intrathecal administration of chloroprocaine 1% and 1 trial testing efficacy and safety of perineural injection of chloroprocaine 2% on about 600 subjects in total. Moreover, another clinical trial assessing the efficacy and safety of chloroprocaine 3% administered via epidural route in parturients and a pediatric study assessing the efficacy and safety of chloroprocaine 1% and 2% for PNB are currently ongoing.
Chloroprocaine proved to be highly efficacious in all the above-mentioned clinical trials, and the very favourable safety profile has been strongly confirmed for the intrathecal and perineural route of administration.
Chloroprocaine 3% proved to be efficacious and well tolerated also in the full package of preclinical studies introduced in section "Non-clinical background information". Moreover, an anaesthesia effect was observed from 5 min after the instillation until 60 min for chloroprocaine 3% gel and this is coherent with the known anaesthetic action of the product and comparable to other ocular topical product tested on animal models both liquid or in jelly formulation.(3)
Importantly, the drug product is topically applied to the site of action and has minimal systemic absorption. The proposed gel formulation contains hydroxyethylcellulose to allow extended contact with the cornea, which is theorized to result in extended anaesthesia. The gel formulation allows a reduction of absorption of the anaesthetic through the nasolacrimal system, thereby resulting in undetectable or negligible systemic exposure of chloroprocaine.

1.2.3 Clinical pharmacology

Topical anaesthetic agents block trigeminal nerve endings in the cornea and the conjunctiva only, leaving the intraocular structures in the anterior segment unanaesthetised.(4)
The sensitive terminations of the fifth cranial nerve are concentrated in the cornea and ciliary body in the anterior part of the eye. These fibers are generally nonmyelinated type A-delta and type C. They are able to transmit the sensations of pain, temperature, and touch, and are blocked by lower concentrations of drugs in comparison with motor fibers. To suppress pain, sensitive nerves have to be blocked by anaesthetic agents along the nerve itself, or at its sensory terminations. Sensory termination block is the most important feature of topical anaesthesia. It involves the inhibition of sodium channels at nerve endings or receptors by the anaesthetic agents, thus blocking the production (and not the transmission) of nervous impulses.(5)
The drug product is topically applied to the cornea. There is little or no measurable systemic absorption.

1.2.4 Pharmacokinetics

Chloroprocaine onset of action is rapid (usually within very few minutes) for infiltration, epidural, spinal anaesthesia and peripheral blocks and the duration of action is short, depending on the route and dosage used (usually not longer than 100 minutes). Chloroprocaine is rapidly metabolized in the plasma by hydrolysis of the ester linkage by the enzyme pseudocholinesterase resulting in the production of two major metabolites that can be considered pharmacologically inactive, i.e. β-diethylaminoethanol and 2-chloro-4-aminobenzoic acid (ACBA).(6)

1.2.5 Pharmacodynamics

The mechanism of action of 2-chloroprocaine is the same of LAs that produce reversible loss of sensation, when applied to nervous tissue. Their primary site of action is the cell membrane and they produce their effect interacting directly with voltage-gated Na+ channels. It is now generally accepted that the mechanism of action of these compounds is based on the interaction with specific binding sites within the Na+ channels resulting in a blockade of the Na+ current. In higher concentrations, the other ion channels (K+, Ca++) might be affected as well.(7)

1.2.6 Clinical efficacy

Similarly to lidocaine, chloroprocaine is used for short duration surgical procedures, mainly in the ambulatory setting, when a fast recovery and prompt home readiness are required.
Based on data obtained from the clinical trials, the data available in literature as well as the post-marketing experience, several aspects underline the importance of chloroprocaine in the clinical practice supporting its reliable efficacy and safety profile.
Chloroprocaine may be advantageous regarding ultra-short and short surgery, matching the important key benefits required for a local anaesthetic of choice in this setting.
In particular, its effects lead to well tolerated and reliable blocks with rapid onset and quick recovery.
As regards the specific development of chloroprocaine gel formulation of ophthalmological indication, it is important to point out that topical ocular anaesthesia is presently administered as oxybuprocaine (in Europe), proparacaine (in US) or tetracaine (both in Eu and US) drops, or lidocaine jelly (in US only). Topical anaesthetic agents are used with or without intravenous sedation. Topical anaesthesia should be reserved for the cooperative cataract patient who, with a dilated pupil, can tolerate the microscope light.
Importantly, during recent years there has been an increase in the off-label use of lidocaine 2% gel for ophthalmic procedures.(8) A majority of these reports reported favourable patient-pain profiles with the use of viscous preparation as the sole anaesthetic agent. This led to development and approval by the Food and Drug Administration of Lidocaine hydrochloride 3.5 % ophthalmic gel (Akten, Akorn Inc.) for ocular surface anaesthesia during ophthalmologic procedures.

1.2.7 Clinical safety

The general overview of safety profile of chloroprocaine comes from large amount of data collected during the development of chloroprocaine 1% formulation indicated for intrathecal block and chloroprocaine 2% indicated for perineural block and also from the post marketing experience.

According to historical and literature evidence, data collected from the clinical studies confirmed the improved safety profile and the more favourable pharmacokinetic properties of chloroprocaine for the intended indications. All adverse events registered in clinical studies were consistent with the known safety profile of chloroprocaine.
As a matter of fact, chloroprocaine is the most rapidly metabolized local anaesthetic currently used. In vitro chloroprocaine half-life is approximately 25 sec and it is cleared efficiently even in former preterm neonates also when receiving high epidural infusion rates.(9, 10) Rapid plasma degradation, rapid onset, lack of accumulation, makes chloroprocaine systemic toxicity less likely compared to other amide-type LAs.(11) Importantly, chloroprocaine is considered the local anaesthetic with the safest toxicological profile compared to other LAs, with a very low liability to induce cardiotoxic effects, due to its broad margin of safety and due to its ultra-rapid metabolism (ester hydrolysis) after systemic resorption. Toxicity due to inadvertent systemic injection as well as toxicity due to absorption of LA may be avoided using the ester-type LA, chloroprocaine.
Plasma concentrations of chloroprocaine and its metabolite ACBA, as well as urinary ACBA excretion, were assessed as secondary endpoint in a phase 2 study, to confirm low systemic exposure to chloroprocaine following intrathecal administration, the most sensitive model to asses systemic toxicity. As expected, chloroprocaine was not detectable in any plasma sample of any patient. On the contrary, the metabolite ACBA was quantifiable in most plasma samples. The results of the study confirm the correlation between the peculiar plasmatic metabolism of chloroprocaine to its well-known safety profile. Indeed, even after administration via spinal route, the drug metabolite ACBA results quantifiable already after 10 minutes, meaning that as soon as chloroprocaine reaches the blood stream, its degradation is almost instantaneous.
Of note, the ultra-rapid plasmatic degradation of chloroprocaine allows to avoid any systemic toxicity risk even in the rare case of inadvertent intravascular injection or unusually rapid absorption in areas with a high density of blood vessels.
Also post marketing data strongly confirms the favourable safety profile of chloroprocaine. Chloroprocaine hydrochloride 10 mg/ml, solution for injection (under the brand names of Ampres®/Clorotekal®/Decelex®), has been commercialized in the EU countries as new chemical entity starting from 2013. No other product with chloroprocaine as active substance for intrathecal administration is present on the European market. Ampres 10 mg/ml, solution for injection is a LA used as one-shot product. According to the clinical practice, no defined daily dose has been established for chloroprocaine HCl because administered dose depends by different factors, such as indication and patient's characteristics. Nonetheless calculations of exposure is based upon estimate number of ampoules sold in EU countries. According to the current European SmPCs for intrathecal use the maximum recommended dose of chloroprocaine hydrochloride in adult population is 50 mg (= 5 ml, one ampoule). Therefore, based on this exposure calculation, during the European and Swiss marketing experience approximately 300'000 patients were treated with intrathecal Chloroprocaine HCl in EU Countries.
In Switzerland, where chloroprocaine is marketed as 0.5%, 1%, 2% and 3% solutions for injection, for local anaesthesia by infiltration, for intravenous anaesthesia, for peripheral nerve block and for epidural block, approximately 250'000 patients were exposed to the drug product till now.
Evaluation of all safety data collected during the European post-marketing experience shows that no newly safety concerns have been identified in relation to the drug product and its safety profile.

1.2.8 Risk and benefits

Expected benefit of anaesthetic gel formulation include:

- Coating of the eye without requiring repeated doses.
- Longer duration than the drops solution due to its viscosity. This permits to obtain a better anaesthesia and higherexposure to the drug.
- Reduced systemic absorption through the nasolacrimal system which translates into a reduced potential for systemic toxicity.
- The majority of patients treated with gel preparations do not suffer from the corneal epithelial and surface irregularities that typically occur due to the toxic nature of other anaesthetic drop preparations.
- Improved lubrication of surgical instruments and easier entry and exit through surgical wounds.

Therefore, while all currently marketed in Europe ophthalmic preparations of topical anaesthesia are in drop solution form, a chloroprocaine gel formulation may represent an improved product that could lead to better anaesthesia.
Chloroprocaine is the ideal anaesthetic for local anaesthesia in patients undergoing short-duration surgeries, because it provides rapid onset of action, adequate potency, predictable duration, fast recovery, and the safest toxicological profile when compared to lidocaine and other LAs.
This led Sintetica to the development of chloroprocaine 3% gel, a preservative-free, single-use ophthalmic preparation, as the sole anaesthetic agent to achieve ocular surface anaesthesia.

Sintetica intends to perform a phase 3 study on patients undergoing cataract surgeryto assess the safety and efficacy of topical anaesthesia using chloroprocaine gel.
This prospective, observer masked, randomised, controlled, equivalence phase 3 study will be conducted in approximately 4 European Countries. We consider that neither intrinsic ethnic factors such as race, genetic polymorphisms and genetic diseases, nor extrinsic ethnic factors such as culture, socio-economical factors, local medical practice and therapeutic approach may affect the efficacy and the safety of the drug product. As reported by internationally recognized guideline (CPMP/ICH/364/96, § 2.5.1) the effect of anaesthesia is dramatic, occurs as expected after treatment and is unlikely to have occurred spontaneously, the success of the anaesthesia can be evaluated with objective assessments. The anaesthetic qualities are related primarily to physicochemical properties of the various compounds.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to assessthe equivalence of chloroprocaine3% gel, Sintetica SA (Test)to tetracaine 0.5% eye drop solution (Reference) in terms of proportion of subjects with a *successful surface anesthesia*,* without any *supplementation***at T4(i.e., just before Intra Ocular Lens implantation)with chloroprocaine compared to tetracaine.

Successful surface anesthesia: the ocular discomfort must be 0 (=No pain or discomfort)or 1 (=Occasional pressure sensation, less than 5 separated times during procedure)without any supplementation at T4.
**Supplementation*: Intra-operative analgesia, including additional LA drops administration,after the beginning of the surgery.

Light sedation before the start of the surgery is allowed for anxious patients, according to surgeon experience.
Patients that will need general anesthesia or additional sedation because of excessive anxiety during the surgery will be excluded from the per protocol analysis, but they will not be considered as failures.

2.2 Secondary objectives

The secondary study objectives are to comparethe clinical efficacy and safety of chloroprocaine 3% gel to those of tetracaine 0.5% eye drop solution.

3 INVESTIGATIONAL PLAN

3.1 Overallstudy design

This will be a prospective,randomized, multi-center, active-controlled, masked-observer, parallel-group, competitive equivalence study.

The first patient first visit (FPFV) is defined as the 1st visit performed at the clinical center by the 1st screened subject (1stsigned inform consent).
The last patient last visit (LPLV) is defined as the last visit performed 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.

3.2 Visit schedule:

- ✓ Selection visit (Day-90/Day-1),
- ✓ Inclusion visit (Day 1/ surgery day),
- ✓ Follow-up visit (Day 2, on site/phone visit),
- ✓ Final visit (Day 8±1),
- ✓ Optionalvisit (Day 28±3, phone visit).

3.3 Discussion of design

The study has been designed to assessthe equivalence of chloroprocaine 3% gel (Test) with respect to tetracaine 0.5% solution (Reference) in surface anesthesia.

In designing the study, the following guidelines were taken into consideration: ICH E9 guideline on Statistical principles for clinical trials; the Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99); and the Points to consider on switching between superiority and non-inferiority guideline (CPMP/EWP/482/99).

With regards to anesthesia, topical has become the most common form for routine cataract. Each patient will be allocated to a treatment arm according to a computer-generated randomization list. Patients in both groups will receive three drops of study products before surgery. (16)

Choice for a masked observer:

- The surgeon will be aware of the treatment administered.
  He will be in charge of instillation of the gel/drop, or a delegate if necessary.
  He will not be further involved in patient's care and data recording for the study, and all the study variables will be evaluated and recorded by another investigator, masked to the formulation applied.
  The surgeon will be only involved in patient surgery and in assessment of surgical performance and surgeon global satisfaction.
- An independent masked investigator will perform screening assessments, assess primary endpoint at D1 (patient discomfort), then patient global satisfaction and Adverse Event at D2 and overall secondary endpoints (clinical efficacy and ocular and systemic safety parameters) for each patient at D8.
- The patient will be masked.

3.4 Study endpoints

3.4.1 Primary endpoint

Theprimary endpoint is the proportion of subjects in each treatment group with a successful surface anesthesia, without any supplementation at the time point T4.
A successful surface anesthesia is equal to 1 and is defined as ocular discomfort equal to 0 (=no pain or pressure) or 1 (=occasional pressure sensation, less than 5 separated times during procedure). It is equal to 0 otherwise (e.g. ocular discomfort > 1).The discomfort of the patient's operated eye will be assessed on the following 6-point ordinal scale:

0. No pain or discomfort
1. Occasional pressure sensation, less than 5 separated times during procedure
2. Occasional burning or stinging sensation, less than 5 separated times during procedure
3. Occasional burning or stinging sensation, more than 5 separated times during procedure
4. Continuous sensation of stinging, burning, or pressure during procedure, tolerable
5. Sensations in point 3 intensified, described as severe or non-tolerable.

Treatments will be assessed at 4 different timepoints of the surgery by a masked observer:

- T1: just before first incision
- T2: end of capsulorhexis
- T3: end of phacoemulsification
- T4: right before IOL implantation.

3.4.2 Secondary endpoints

Clinical efficacy during surgery

- Successful surface anesthesia at T1, T2 and T3 based on patient questioning aboutthePatient's operated eye discomfort, on the same 6-point ordinal scale.
- Time to obtain sufficient anesthesia (use of forceps).
- Total time of anesthesia
- Blinking reflex dropping a water drop at the end of the surgery
- Number of supplemental drops necessary for obtaining and/or maintaining anesthesia
- Supplementary treatments (general anesthesia or intra-operative systemic analgesia,necessary for obtaining and/or maintaining, anesthesia
- Total surgical time (time between the first incision and the end of surgery, corresponding to eye lid speculum removal)
- Assessment of surgical comfort by the surgeon at each stage of the surgical procedure.

  (0) = uncomplicated
  (1) = slightly complicated
  (2) = complicated

- Assessment of the global efficacy by the surgeon for anesthesia.
  (0) = Very satisfactory
  (1) = Satisfactory
  (2) = Unsatisfactory
  (3) = Very unsatisfactory

Ocular and systemic safety

- Ocular symptoms: pain, irritation/burning/stinging, photophobia, foreign body sensation.

  The ocular symptoms will be graded by the patient according to the following scale:

  (0) = Absent
  (1) = Mild
  (2) = Moderate
  (3) = Severe

- Objective ocular signs (Slit Lamp Examination):palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, follico-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells and flare, and other objective ocular signs.

  (0) = None
  (1) = Mild
  (2) = Moderate
  (3) = Severe

- Slit lamp examination and fluorescein test
- Endothelial cells count (specular microscopy)

- Cornealthickness (pachymetry)
- Best far corrected visual acuity
- Funduscopy
- Intra-Ocular Pressure
- Vital signs (blood pressure and heart rate)
- Adverse eventsoccurrence
- Surgeon satisfaction "How do you consider the study product global tolerance?'':

  (0) = Very satisfactory
  (1) = Satisfactory
  (2) = Unsatisfactory
  (3) = Very unsatisfactory
- Patient global satisfaction at D1 based on a 5-question questionnaire read by a masked observer.

4 STUDY POPULATION

4.1 Target population

The study population will consist ofapproximately 342 evaluable subjects who will have to undergo cataract surgery in a single eye at a time.
In case both eyes have to be operated, the patient could be included in the study only if both eyes are operated separately.
The eye that will be randomized in the study will be the first eye that will be operated based on investigator decision.
The second eye could be operated 7 days after the end of the study (that means 14 days after the surgery).

4.2 Inclusion criteria

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

1. Signed and datedinformed consent
2. Male or femaleaged ≥ 18 years
3. Senile or pre-senilecataract
4. Scheduled to undergo cataract surgery in a single eyeat a time (clear corneal self-sealing incisions - phacoemulsification – foldable intra-ocular lens surgery with injector)

4.3 Exclusion criteria

Subjects meetingONE OR MORE of the following criteria at the selection visit will not be enrolled in the study:

Ophthalmic exclusion criteria

- Surgical conditions in the eye to be operated:

1. Combined surgery
2. Previous intraocular surgery
3. Previous corneal refractive surgeries less than 6 months before screening

- Non-surgical conditions in the eye to be operated:

4. Non Senile or non pre-senilecataract (e.g.: traumatic, pathological or congenital cataract)
5. Pupillary abnormalities (irregular, etc.)
6. Iris synechiae
7. Eye movementdisorder (nystagmus, etc.)
8. Dacryocystitis and all other pathologies of tears drainage system
9. History of Inflammatory ocular disease (Iritis, uveitis, herpetic keratitis)
10. Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration and superficial punctuate keratitis)
11. History of ocular traumatism, infection or inflammation within the last 3 months
12. Pseudo-exfoliation, exfoliative syndrome
13. Prior intravitreal injections within 7 days of the surgery
14. Intra Ocular Pressur over 25mmHg under treatment

- Ophthalmic conditions in the contra-lateral eye:

15. Best corrected visual acuity < 1/10
16. Patient already included in the study for phakoexeresis
17. History of ophthalmic surgical complication (cystoid macular oedema, etc.)

Systemic/non ophthalmic exclusion criteria

- General history:

18. Diabetesmellitus
19. Surdity
20. Parkinson disease
21. Excessive anxiety
22. Any other medical or surgical history, disorder or disease such as acute or chronic severe organic disease: hepatic, endocrine neoplasic, hematological diseases, severe psychiatric illness, relevant cardiovascular abnormalities (such as unstable angina, bradycardia, atrial fibrillation,uncontrolled hypertension: systolic blood pressure over 140mm Hg, diastolic blood pressure over 90mmHg) and/or any complicating factor or structural abnormality judged by the investigator to be incompatible with the study.

- Allergic history:

23. Known hypersensitivity to sulfonamides products or any of the components of the study medications or to test products

Specific exclusion criteria for women

24. Pregnancy (positive pregnancy test), lactation
25. Women of childbearing potential without an acceptable effective method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant)until end of the study participation

OR

26. Women not hysterectomized, not menopaused nor surgically sterilized.

Exclusion criteria related to general conditions

27. Inability of patient and/or relatives to understand the study procedures and thus inability to give informed consent
28. Non-compliant patient and/or relatives (e.g. not willing to attend the follow-up visits, way of life interfering with compliance)
29. Participation in anotherclinicalstudy
30. Already included once in this study

31. Ward of court
32. Patient not covered by the Social Security

Exclusion criteria related to previous and concomitant medications / non-product therapies
Patient using any of the following previous and concomitant medication / treatment (according to the described periods) will not be included in the study:

<table>
<tr><td colspan="5">NOT ALLOWED CONCOMITANT MEDICATIONS</td></tr>
<tr><td colspan="3">Before the surgery</td><td>Surgery</td><td>After surgery</td></tr>
<tr><td>30 days</td><td>15 days</td><td>7 days</td><td>Day 1</td><td>Day 2 to Day 28</td></tr>
<tr><td colspan="5">Any change in concomitant anti-depressant medication ……………………………………………</td></tr>
<tr><td></td><td colspan="4">Systemic opioids and morphinic drugs ....</td></tr>
<tr><td></td><td colspan="4">Topical ocular treatment with anaesthetic action*…………………………….</td></tr>
<tr><td colspan="2"></td><td colspan="3">Prior intravitreal injections ………………………………..</td></tr>
<tr><td colspan="2"></td><td colspan="3">Sulfonamides products,,
Others systemic antalgics drugs (except paracetamol)..............</td></tr>
<tr><td colspan="2"></td><td colspan="3">Any change in other systemic medication already ongoing before selection visit</td></tr>
</table>

**except the pre-, peri-operative and post-operative therapeutics procedure to be followed according to the protocol.*

4.4 Withdrawal criteria

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the type of discontinuation and the primary reason for discontinuation will be recorded.
In case of lack of efficacy of the investigational products, the patient will be regarded as not having had a successful anesthesia. The patient will not be discontinued from the study.

Patients who will present per-operative complications preventing primary endpoint assessment to be performed, will be withdrawn from the efficacy analysisand the standard treatment of the hospital will be applied.

However, these patients will be followed for safety parameters assessments.

The complications are the followings:

- Capsular rupture.
- Zonular disinsertion.
- Vitreous exit.
- Residual mass.
- Implantation localised in the sulcus.
- Implantation localised in the anterior chamber.
- Long-lasting surgery (more than 30 minutes)

Moreover, if, in the opinion of the investigator, there is any other situation or condition which puts the subject at significant risk patients should be withdrawn from the study too.

Any patient may voluntarily discontinue the study at any time he or she chooses (Declaration of Helsinki), without prejudice. The investigator may elect to discontinue a patient for reasons related to the study product (AE or unsatisfactory therapeutic response). In either event, details should be recorded on the patient source data and CRF and reported separately.

Possible reasons for withdrawal include the following:

- AEs leading to discontinuation from the study.
- Patient's request.
- The patient is lost to follow-up: investigator must contact his/her patient to obtain more information (by phone, fax, regular mail or email…).

If a patient discontinues prematurely the study after randomisation, the investigator will perform all the investigations planned at the final visit (visit 4).

4.4.1 Discontinuation procedures

For any subject discontinuing from interventions and findings, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (Visit 4) to examine the subject's health conditions
- arrange for alternative medical care of the withdrawn subject, if necessary
- report in the source data and CRF date and time of the investigational product administration, and date and primary reason of study discontinuation
- record in the source data and CRF any follow-up, if the subject is withdrawn for an AE

Discontinued subjects will not be replaced.

5 CLINICAL SUPPLIES

5.1 Study Treatment

5.1.1 Description of products

The analytical certificates will be enclosed with the investigational medicinal products (IMPs).

5.1.1.1 Test product

TEST (T)	
IMP	Chloroprocaine 3%
Distributor	Sintetica S.A., Switzerland
Manufacturer	Laboratoire Unither, France
Pharmaceutical form	Gel
Dose	1 drops
Frequency	3 times
Administration route	Topical instillation

5.1.1.2 Reference product

REFERENCE (R)

IMP	Tetracaine 0.5%
Active substance	Tetracaine
Distributor	Bausch &Lomb UK Ltd
Pharmaceutical form	Solution
Dose	1 drops
Frequency	3 times
Administration route	Topical instillation

5.1.2 Dose regimen

Patients will be randomized to one of the two treatment groups to receive either chloroprocaine 3% gel (Test) or tetracaine 0.5% solution (Reference) as topical anesthetics in phacoemulsification before surgery, according to the randomized, parallel-group design of the study.

For Chloroprocaine 3% and Tetracaine 0,5% administration: **three IMP drops instillation as follow:**

- 1st Drop instillation, then wait for 5 minutes
- Eye Disinfection, then wait for 2 minutes
- 2nd Drop instillation, then wait for 1 minute
- 3rdDrop instillation, then wait for 1 minute
- Start of Surgery.

Details on the IMP preparation before installation will be given in the study manual.

5.1.3 Investigational product distribution

The test and reference products will be administered by the surgeonor by his/her delegate. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

5.1.4 Packaging and labelling

Packaging and labelling will be carried out by the Sponsor according to the randomization list. All labels will be written in the local language. The content of the labelling is in accordance with the GMP specifications, according to the Annex 13 to the Good Manufacturing Practice and local requirements.

5.1.5 Storage conditions

The test product will be stored at 15 - 25°C in a dry locked place, sheltered from light. The reference product will be stored at < 30°C and must not be frozen.
Further details about study drug preparation and handling are reported in the IMP Manual provided to the investigators.

5.1.6 Drug accountability

The test and reference investigational products will be provided directly to the investigator by the sponsor.

After receipt of the investigational products supply, the pharmacist or the person identified as the recipient of the study drug supply will confirm receipt throught the IRT system.

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

5.2 Randomization

Patients will be centrally allocated to one of the two treatment groups by a dynamic minimization procedure stratifying bycenter. The dynamic minimization will use a stochastic treatment allocation algorithm based on the variance method.

5.3 Treatment allocation

Patients will be allocated to the Test (chloroprocaine) arm or Reference (tetracaine) arm in a 1:1 ratio.

Each study center will receive a set of Test and Reference treatments. Each treatment unidose will be individually labelled and packaged (see section 5.2).

5.4 Masking

This is a masked-observer study.

- The surgeon placing the gel/drop will be aware of the treatment administered. He/She will not be further involved in patient's care, and data recording and all the study variables will be evaluated and recorded by another investigator, or his/her deputy, masked to the formulation applied.
The surgeon will be only involved in patient surgery and in satisfaction assessment.
- An independent masked investigator will evaluate sensory block and safety parameters for each patient.
- The patient will be masked.

The masking of the trial will be maintained for the entire duration of the study for the masked observer until database lock.However, participants may be unmasked during the trial for the occurrence of a medical emergency.

Each IMP kit will be numbered according to a randomized kits list created by IDDI masked team and provided to supplier before the start of the study. The tracking, delivery and allocation of IMP kit numbers will be handled throught the IRT system.
In case of emergency the investigator will connect the IRT system to perform a code break, revealing the treatment received by the patient and the exact content of each kits allocated to this patient. The investigators will be trained to the code break procedure at the beginning of the study and a user manual will be available for download into the IRT for the whole study lifecycle.

5.5 Other Treatments

No other drugs than Test and Reference products will be provided for the study.
Patients included in the study will undergo the following medical care before surgery, the day of surgery and after surgery, according to site practice.

Patients will be asked to stop their authorized ocular treatments the day before the surgery.

Preparation of surgery:

- In case ofanxious patients, the use of light sedation is allowed before the start of the surgery.

  The aim is anxiolysis without deep sedation, as patient are at risk of moving if they suddenly wake up. To prevent over sedation, small doses should be used and verbal contact maintained during surgery.

  Type of product that can be use: benzodiazepine drugs (e.g.: Midazolam, due to its short action time and short plasmatic half-life).
- Eye disinfection according to sites practice,using topical antiseptic (e.g.: Povidone iodine 4% (on the skin) and ophthalmic Povidone iodine (ocular irrigation)) in order to keep the asepsis condition of the surgical area
- Pupil dilatation: according to site practice, using mydriatic products that must not contain any analgesic.
- Intraocular injectionof Ophthalmic viscoelastic:according to site practice,using products that must not contains any analgesic.
- Intraocular irrigating solution: balanced salt solution (BSS) only.
- Before start of the surgery, use sterile forceps to pinch bulbar nasal conjunctiva, once the operative drape is in place.
  It is of high importance that the patient does not see the forceps precisely.
  This procedure is to be performed with the drape on, under the light of the microscope.
  If the pinch to the conjunctiva is painful, then additional LA drops administration or intravenous analgesia using an analgesic with short duration of action and rapid elimination (e.gAlfentanyl),is to be performed according to surgeon decision, to decrease pain perception during surgery.

During the surgery:

- The incision length must be adapted to the size of the implant chosen by the surgeon (according to instructions for use) so that the pressure applied on the eye ball during implantation is not excessive.
- Injection into the capsular bag at the last step of cataract extraction of antibiotic drug (e.g.: 0.1 ml cefuroxime solution at the concentration of 10 mg/ml prepared in sterile conditions with saline 0.9% (15)).
- In case of excessive dilation of the pupil at the end of surgery (≥ 8mm after IOL injection and washing of viscoelastics), use of a miotic substance will be left to the investigator's surgical habits.

- General anaesthesia or additional light sedation could be used during surgery in case of situations in which anxiety and/or movement of the patient prevents the investigator from performing the procedure in a sufficiently safe manner.

  In that case, patients will be excluded from per protocol analysis but will not be considered as failure.

After surgery

Post operative surgery follow-up will be conducted in accordance with sites current practices, using usual anti-inflammatory, corticosteroid and antibiotic drugs.
Here is a list of class of postoperative drugs that could be used at each site for patient care according to sites practices:
- Antibiotics (e.g.: Tobramycin, Azythromycin).
- Corticoid (e.g.: dexamethasone).
- Non-steroid anti-inflammatory drugs (e.g.: Indomethacin, Ketorolac, Flurbiprofen) after surgery.

6 STUDYCONDUCT

The study procedures and their implantation schedule are summarizedin Table 1.

6.1 Study visits

The study protocol foresees one study treatment for each patient, followed by post-operative recovery and discharge.Maximum study duration will be approximatively28 days.

The study will include a Selection visit (Visit 1 - Day -90/Day -1), an Inclusion visit (Visit 2 - Day 1/surgery day), a Follow-up visit (Visit 3 - Day 2, phone call), a finalFinalvisit (Visit 4 - Day 8), and anOptionalvisit in case of AEat visit 4 (Visit 5 - Day 28, phone call):

- **Screening phase**
  - Selection-Visit 1: between Day -90 and Day -1. The procedures will be conducted by the masked-observer.
    - Patient information about the aims, procedures and possible risks of the study and signature of the informed consent form before any study related procedures
    - Urine pregnancy test
    - Recording of demography data
    - Ocular and systemic medical and surgical histories
    - Previous and concomitant ocular and non-ocular treatments
    - Ocularsymptoms
    - Best-far corrected visual acuity in both eyes
    - Slit lamp examination and fluorescein test
    - IOP in both eyes

- Endothelial cell count by specular microscopy
- Funduscopy
- Pachymetry
- Macular optical coherence tomography
- Cardiovascular parameters (blood pressure and heart rate)
- Verification of the study inclusion/exclusion criteria

➢ **Interventional phase**

▪ Inclusion - Visit 2: Day 1 (surgery day). The procedures will be conducted by the surgeon except the assessement of primary criteria and the check of cardiovascular parameters that will be carried out by the masked-observer.

- Before anesthesia, patient's questioning about previous and concomitant ocular and non-ocular treatments
- Verification of the study inclusion/exclusion criteria
- Urine pregnancy test (only if Visit 2 is more than 30 days after visit 1)
- AEs occurrencesincepreviousvisit
- Patient's allocation in one of a treatment group (chloroprocaine 3% gel (Test) or tetracaine 0.5% eye)
- Cardiovascular parameters monitoring (blood pressure and heart rate)
- Patient discomfort assessment at T1 with forceps (just before the first incision), T2 (end of capsulorhexis), T3 (end of phacoemulsification), and T4 (just before Intra Ocular Lens implantation)
- Surgical performance assessment
- Surgeon global satisfaction assessment
- Dose-regimen compliance

➢ **Follow-up phase**

▪ Follow-up - Visit 3: Day 2 (on-site visit or phone visit according to site current practice). The procedures will be carried out by the masked-observer.

- Patient's questioning about concomitant ocular and non-ocular treatments
- AEs occurrence
- Patient global satisfaction (questionnaire read by masked-observer)of the surgery.

▪ Final Visit - Visit 4: Day 8 ± 1 dayon-site visit. The procedures will be carried out by the masked-observer.

- Patient's questioning about concomitant ocular and non-ocular treatments
- Ocular symptoms
- Best-far corrected visual acuity in both eyes

- Slit lamp examination and fluorescein test
- IOP in both eyes
- Endothelial cell count by specular microscopy
- Funduscopy
- Pachymetry
- Cardiovascular parameters (blood pressure and heart rate)
- AEs occurrence

If AE occurred during Follow-up of the study (between Day 1 and Day 8, an optional visit will be performed at day 28 (phone call).

- Optionalvisit – Visit 5: Day 28 ± 3 days (phone visit). The procedures will be carried out by the masked-observer only in case of AE on-going at V4.
  - Patient's questioning about concomitant ocular and non-ocular treatments
  - AEs occurrence

- Premature Discontinuation Visit

If premature discontinuation occurs before randomization, assessments of visit 2 (until before randomization) are to be performed.

If premature discontinuation occurs after randomization, assessments of visit 4 are to be performed.

6.2 Diet and lifestyle

Study participants will undergo study procedures as outpatients (day case surgery). Patients will arrive at the clinical center in the morning of the scheduled surgery dayand will be discharged in the evening of the same day, except in the event of unforeseen complications or safety concerns.

6.3 Study procedures

6.3.1 Efficacy measures

6.3.1.1 Patient's discomfort assessement during surgery

The discomfort of the patient's operated eye will be assessed on a 6-point ordinal scale at 4time points during surgery:

- 0: No pain or discomfort
- 1: Occasional pressure sensation, less than 5 separated times during procedure
- 2: Occasional burning or stinging sensation, less than 5 separated times during procedure
- 3: Occasional burning or stinging sensation, more than 5 separated times during procedure
- 4: Continuous sensation of stinging, burning, or pressure during procedure, tolerable
- 5: Sensations in point 3 intensified, described as severe or non-tolerable.

Based on the aforementioned scale, successful surface anaesthesia is defined as no pain/discomfort (scale=0) or occasional pressure sensation,less than 5 separated times during procedure (scale=1).

The discomfort of the patient's operated eye will be assessed at4 different timepoints of the surgery:

-T1: just before first incision
-T2: end of capsulorehexis
-T3: end of phacoemulsification
-T4: right before Intra Ocular Lens implantation

6.3.1.2 Blinking assessement

- At the end of surgery: the blinking reflex will be assessed by dropping a water drop.

6.3.1.3 Anesthesia assessement

- Time to obtain sufficient anesthesiaassessed with forceps (after 3rd drop instillation, just before start of surgery):
- Total time of anesthesia:from the instillation of the 3 drops of chloroprocaine 3% gel (Test) or tetracaine 0.5% (Reference) to the end of surgery (end of anesthesia assessed with forceps, every 5 minutes from the end of surgery): To assess the duration of anesthesia, the testing will be concluded when the study subject reported 'pain' on two successive tests with 5 minutes in between.
- Number of supplemental drops necessary for obtaining and/or maintaining anesthesia
- Supplementary treatments (general anesthesia or intra-operative systemic analgesia) necessary for obtaining and/or maintaining anesthesia

6.3.1.4 Total Surgical Time (using chronometer)

It is the total time between the first incision and the end of surgery, corresponding to eyelid speculum removal.

6.3.1.5 Surgeon assessments

- Surgical confortassessement at each stage of the surgical procedure (T1, T2, T3 and T4):
  (0) = uncomplicated
  (1) = slightly complicated
  (2) = complicated

- Global efficacy assessemeent for anesthesia:
  (0) = Very satisfactory
  (1) = Satisfactory
  (2) = Not very satisfactory
  (3) = Unsatisfactory)

6.3.2 Safety measures

6.3.2.1 Ocular and systemic tolerability assessment at visit 1 and visit 4

- Ocular symptoms: pain, irritation/burning/stinging, photophobia, foreign body sensation. The ocular symptoms will be graded by the patient according to the following scale:
  (0) = Absent
  (1) = Mild
  (2) = Moderate
  (3) = Severe
- Objective ocular signs (Slit Lamp Examination): palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, follico-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells and flare, and other objective ocular signs.
  (0) = None
  (1) = Mild
  (2) = Moderate
  (3) = Severe

6.3.2.2 Endothelial cells count (specular microscopy) at visit 1 and visit 4

The number of endothelial cells count will be performed in the central cornea with specular microscopy and will be reported in cell/mm2.

6.3.2.3 Corneal thickness (pachymetry) at visit 1 and visit 4

Measurement of the central corneal thickness will be performed with a pachymeter

6.3.2.4 Best far corrected visual acuity at visit 1 and visit 4

Far BCVA will be measured on both eyes using the same chart throughout the study.

6.3.2.5 Fundoscopy at visit 1 and visit 4

Fundus examination in both eyes: any detected abnormalitywill be recorded.

6.3.2.6 Slit lamp examination at visit 1 and visit 4

The following ocular signs will be evaluated at the slit lamp examination on a 0-3 scale:

- Blepharitis
- Eyelid oedema
- Iris pigmentation modification
- Abnormal eyelashes aspect
- Folliculo-papillary conjunctivitis
- Other ocular abnormality.

6.3.2.7 Corneal fluorescein staining at visit 1 and visit 4

Approximately 2-3 minutes following fluorescein instillation, corneal staining will be evaluated in both eye, using a slit lamp, based on the Oxford scale (grades of 0-5). See appendix 1.

6.3.2.8 Intra-Ocular Pressure at visit 1 and visit 4

IOP will be assessed according site current practice (air puff or applanation tonometer); the same measurement is to be used for the same patient throughout the study.

6.3.2.9 Vital signs measurements (blood pressure, heart rate)

Will be assessedat visit 1 and visit 4 andmonitored during the surgery)

6.3.2.10 Surgeon satisfaction "How do you consider the study product global tolerance?":

(0) = Very satisfactory
(1) = Satisfactory
(2) = Not very satisfactory
(3) = Unsatisfactory

6.3.2.11 Patient global satisfaction at Follow-up visit(Visit 3 - D2)

Based on a question read by a masked observer, with 5 possible answers (Likert satisfaction scale) to assess the patient satisfaction about the overall anesthesia during the surgery:
"Overall, how satisfied are you with the topical study product used for your local anesthesia during your cataract surgery?"

- Verysatisfied
- Globallysatisfied
- Neithersatified, norunsatisfied
- Globallyunsatisfied
- Veryunsatisfied

The patient will have the opportunity to add any comment to complete his/her answer.

6.3.2.12 Adverse events recorded throughout the study

Surgery-related pain at the site of surgery will not be recorded as an adverse event, but assessed as traitement success or failure.
A brief summary of AE definition, classification and management is reported below.

6.3.2.13 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 authorized use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorization, 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 thesignature of theinformed consentand before the first medicinal product administration
- new measurements(vital signs, ECG, laboratory parameters, etc.), performed after thesignature of theinformed consentand before the first medicinal product administration, which show aclinically significant worseningin comparison with a previous (baseline)measurement performed after thesignature of theinformed consent
- any disease diagnosedafter the anamnesis recorded at visit 1and before the first medicinal product administration
- physical and mentalstatus changes(pre-syncope, anxiety, dizziness, fainting, etc.) occurred after thesignature of theinformed consentand 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 hospitalization or prolongation of existing hospitalization
  - 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 hospitalization; 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, the Investigator's Brochure (IB) for the test formulation and the SmPC for the reference formulation 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.

6.3.2.13.1.1 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.

6.3.2.13.1.2 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 in the source documents and later transcribed into the CRF:

1. Adverse Event: progressive number of the adverse event or progressive number of follow-up of the adverse event
2. Description: verbatim description of the adverse event
   Start Date/Time: start date/time of the adverse event or
   Follow-up Date/Time: follow-up date/time of the adverse event
3. End Date/Time: end date/time of the adverse event
4. Affected Body Area: anatomical location relevant for the event; in case of an ophthalmological AE, then it needs to be recorded whether or not it is the study eye
5. Whether the adverse event start before or after the first intake of the study drugor whether the adverse event has worsened or not after the first intake of the study drug
6. 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.
7. Investigator's opinion about the reasonable possibility of a causal relationship with the study drug.
8. Investigator's opinion about other causal relationship (e.g. non study drug, concomitant therapy, study device, etc.).
9. Severity: the severity or intensity of the event
   1 Mild
   2 Moderate
   3 Severe
10. Pattern: Used to indicate the pattern of the event over time
    1 Single Event
    2 Continuous
    3 Intermittent
11. Serious Adverse Event
12. 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
13. Concomitant Therapy: if a concomitant therapy is given, it must be reported in the specific CRF forms

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

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

16. Outcome: Outcome of the event

1 Recovered/Resolved
2 Recovered/ResolvedwithSequelae
3 Recovering/Resolving
4 Not Recovered/Not Resolved
5 Fatal
6 Unknown

6.3.2.13.1.3 SAEs reporting

The pharmacovigilance will be under the control of the Sponsor, Sintetica SA.
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, when required. 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 on the report.
The sponsor will evaluate the SAE expectedness on the basis of the RSI.

6.3.2.13.1.4 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 studynumber
- One identifiable codedsubject
- One identifiable reporter
- One SUSAR
- One suspect IMP (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).

6.3.2.13.1.5 Otherevents 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.

6.3.2.13.1.6 SAEs: contacts

The Pharmacovigilance can be contacted using the phone and fax numbers stated in this protocol.

SAEs must be reported on SAE reporting forms and faxed/emailed within 24 H to sponsor - contact details below:

Corporate Drug Safety Unit
Fax: +41(0)91.646.85.61 - Phone: +41(0)91.640.42.50
Email: corporate_drug_safety@sintetica.com

6.4 Description of specificprocedures

6.4.1 Procedures for post-operative recovery

At the end of the surgical procedure, patients will be moved to the post-operative recovery room, where they will stay until the criteria for discharge are met according to the hospitals' standard procedures. In general, to be discharged patients must have a score ≥ 9 on the modified Aldrete's scoring scale for day case surgery and no pain. Hemodynamic variables must be stable and SpO_2 must be acceptable (> 92%) without oxygen therapy. Patients will be asked about any adverse events, and to possible allergic reactions (e.g. urticaria). If all the criteria are met and no adverse reactions occur, the patient will be discharged.

6.4.2 Procedures for telephonic follow-up

On Day 1 and on Day 28 (± 3 days) after surgery, a deputy of the Investigator, not aware of the administered treatment, will contact the patients by telephone and will question them about any adverse reactions which might have occurred after discharge, with particular attention to any

sign of late systemic toxicity, local toxicity, neurological symptoms and allergic reactions.Concomitant ocular and non-ocular treatments will also be assessed on these days. A questionnaire on patient global satisfaction will be read by a masked observer on D1.

7 STATISTICAL METHODS

Data documented in this study and the parameters measured will be evaluated and presented using descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values for quantitative variables, and absolute and relative (%) frequencies for qualitative variables. The statistics will be reported by treatment group. For the variables recorded for both eyes, the statistics will be reported by treatment group, separately for the eye to be operated and for the other eye. Confidence intervals will be reported, where appropriate. If not stated elsewhere, these intervals will be two sided in each case and provide 95% confidence.
Efficacy will be evaluated in the operated eye using mixed effects models (adjusting for center and country using random effects).

Not available data will be evaluated as “missing values”.A statistical analysis plan (SAP) will be provided before database closure. The statistical analysis will be performed using RStudio v. 1.2.5001 and/or IBM SPSS Statistics v. 25 (or newer) for Windows.

7.1 Analysis Sets

The following analysis sets will be considered:

Safety set: All patients enrolled in the study, for whom there is evidence that they used study medication and for whom any follow-up information is available.

Full Analysis Set (FAS): All patients enrolled in the study for whom any follow-up efficacy information is available.

Per Protocol Set (PPS): All patients of the FAS who did not show any major protocolviolation.

The exclusion of patients from the analysis sets will be discussed during a blind review meeting that will be held before database lock.

The statistical analysis of the onset data and of efficacy will be performed on the basis of the FAS and the PPS. The primary population for the assessment of efficacy will be the PPS, while the statistical analysis on the FAS population will be considered as sensitivity analysis. If there are any major discrepancies between the results of the 2 analyses, they will be the subject of explicit discussion and interpretation. The analysis of safety will be performed on the basis of the safety set.Patients who will present per-operative complications preventing primary endpoint assessment to be performed, will be withdrawn from the efficacy analysis and the standard treatment of the hospital will be applied. Such patients' characteristics will be tabulated and compared with the characteristics of the rest of the patients (i.e. patients who will not present per-operative complications) to investigate potential between group differences.

7.2 Sample size and power considerations

Given the followingdefinitions:
π_E = Proportion of success: Experimental treatment (Chloroprocaine 3% gel formulation);
π_S = Proportion of success: Standard treatment (Tetracaine 0.5% eye drop);
$\epsilon = \pi_E - \pi_S$ (difference between Experimental and Standard treatment proportion of success);
d = Equivalence margin.

The sample size for the two-sided equivalence hypothesis test:

H_0: $|\epsilon| \geq d$ vs. H_A: $|\epsilon| < d$

can be computed according to the formulas:

$N_S = \text{ceiling } \{[(Z_{1-\alpha} + Z_{1-\beta/2})^2 / (|\epsilon| - d)^2] * [\pi_E \text{ x } (1 - \pi_E)/k + \pi_S \text{ x } (1 - \pi_S)]\}$ and

$N_E = k * N_S$[18]

where:

k = Balancing ratio between the two treatment arms (k=1 for balanced group)

N_E = Number of subjects included into the per protocol set for the Experimental treatment (Chloroprocaine 3% gel formulations);

N_S = Number of subjects included into the per protocol set for the Standard treatment (Tetracaine 0.5% eye drop).

In such anequivalence study, sample size depends on the type I error (α) (which is usually set equal to 0.05), the type II error (β) (set equal to 0.20 for the present trial, corresponding to a power of 80%), the equivalence margin d and the expected proportion of success in both treatment groups. In such trials, sample size increases as α and/or β and/or d decrease. The expected proportion of success and the equivalence margin d is estimated based on studies carried out in the past, whose results are reported in the literature. In our case, no such study was available. Nevertheless, we would expect an equivalence margin d to range between 0.05 to 0.15.

To interpret the aforementioned range for the margin d, the estimate of d=0.10 corresponds to a difference in efficiency of 20%. The margin d=0.15 corresponds to a stricter difference in efficiency of 30%. Since there were no previous results available in the literature for our case, we tried different parameter values to check how they affect the estimated sample size. Table 2 provides the estimates for sample size per arm, given that the type I error (α) is set equal to 0.05 and assuming that the expected proportion of success is set equal to 90% for both treatment arms. Note, that in the last column of Table 2 we provide the sample size estimates per arm given that there would be an exclusion rate equal to 10%, which is typical in such a study.

Table 2 Sample size per arm: type I error (α)=0.05 and expected proportion of success =90%, for both treatment arms

Type I error (α)	Type I error (β)	Equivalencemargin d	Sample size per arm	Sample size per arm adjusted for a 10% exclusion rate
0.05	0.20	0.10	155	171

As shown in Table 2, for the expected equivalence d=0.10, the estimated sample size is 171subjectsper group, after adjusting for a possible exclusion rate of 10%. Taking these results into account along with the fact that in the literature we could not find studies that tested topical anaesthesia in cataract surgery enrolling more than about 200 patients overall, we suggest to enrol 171patients per arm, i.e. 342patients overall. Such a sample size would allow for a robust and reliable estimate of the clinical efficacy of 3% chloroprocaine gel and tetracaine 0.5% eye drop as topical anaesthesia in phacoemulsification.

7.3 Handling of missing data

7.3.1 Methods for replacing missing data

- Multiple imputation (MI) under missing at random (MAR) assumption: multiple imputation is a general approach to the problem of missing data that aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. Missing at random (MAR) approach assumes that any systematic difference between the missing values and the observed values can be explained by differences in observed data. The use of multiple imputation under MAR assumption provides unbiased estimations of the parameters and allows evaluating the uncertainty of parameters' estimation due to the presence of missing data. Separate multiple imputations will be performed for each treatment arm.
- Missing as Failure (MF): missing values of the primary end-point are considered as block failures regardless of the treatment arm.
- Worst Case (WC): missing values of the primary end-point are considered as block failures if the patients receive Test product and as block successes if the patients receive Reference product.

7.3.2 Replacement rules for each analysis set

- FAS: missing data of the primary end-point (if any) will be replaced according to MI under MAR assumption method, MF method and WC method in three different sensitivity analyses. Missing data of the secondary end-points will not be replaced.
- PPS: all missing data will not be replaced.
- Safety set: all missing data will not be replaced.

7.4 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarized in contingency tables. Quantitative data will be summarized using classic descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values.

7.5 Analysis of efficacy parameters

The efficacy analysis will be performed on the PPS set (primary efficacy analysis) and FAS (sensitivity analysis). The primary endpoint of the study is defined as the proportion of subjects in each treatment group with a successful surface anesthesia, without any supplementation at the time point T4.
Since randomization will take centers into account, centers need to be accounted for in the statistical analysis. Therefore, mixed effects analysis will be used adjusting for potential centers and/or country effect using random effects models. Specifically, since the primary endpoint concerns proportions, mixed effects logistic regression will be performed, in which the log odds of the outcomes are modeled as a linear combination of treatment and random effects account for potential clustering.
If βis the coefficient that corresponds to mixed effects model treatment effect, then the null hypothesis under investigation is[19]:

$$H_0: |\beta| \geq d \text{ vs. } H_A: |\beta| < d,$$

which correspond to:

$$H_0: \beta \geq d \text{ or } \beta \leq -d \text{ vs. } H_A: \beta < d \text{ or } \beta > -d \ .$$

The two test statistics are computed as:

$$t_1 = \frac{\hat{\beta} - d}{\widehat{SE_\beta}} \quad \text{and} \quad t_2 = \frac{\hat{\beta} - (-d)}{\widehat{SE_\beta}} \quad ,$$

where $\hat{\beta}$ and $\widehat{SE_\beta}$ are the estimated treatment effect and its associated standard error from the mixed effects model. The overall null hypothesis that the treatment effect β falls outside the equivalence interval is rejected if both test statistics are rejected:

$$t_1 \leq -t_{\alpha,\, df} \text{ and } t_2 \geq t_{1-\alpha,\, df},$$

where *df* refers to the appropriate degrees of freedom from the mixed effects model.

7.6 Safetyand tolerability evaluation

- **AEs**

Adverse events (AEs) are described analytically in 6.3.2 and 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 IMP and not worsening after the first dose of IMP
- TEAEs: all AEs occurring or worsening after the first dose of IMP

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, relationship to treatment and severity.

- **Physical examination**

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see section6.3.2.12), will be recorded in the subject source documents.Date of the physical examination andoverall investigator's interpretation (as normal, abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF.

- **Vital signs**

Values of vital signs will be listed and summarized by descriptive statistics.

8 DATA MANAGEMENT PROCEDURES

8.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the electronic CRFs. He must also check that the data reported in the eCRFs correspond to those in the subject's source documents.

8.2 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 3-letter country code (ITA, ESP, SVK), the center number (301, 302, …), and the 3-digit patient number (001, 002, …).

8.3 Data management

Data management will be performed by IDDI under the responsibility of the sponsor. The sponsor will provide the investigator site with a web base electronic data capture (EDC) system

that is fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to EDC system until they have been trained on the EDC system.

Adverse events and medical history will be coded using MedDRA.
Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Dictionary.
Data queries will be raised for inconsistent, implausible or missing data which will allow for modification or verification of the entered data by the investigator staff. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been declared to be cleaned, validated and coded, the database will be locked and the treatment codes will be unblinded to be made available for data analysis.

9 STUDY MONITORING AND AUDITING

9.1 Monitoring

The monitoring visits will be conducted by appropriate staff of Iris Pharma and its representatives, Link Neuroscience and health Care and of the Sponsor. Two monitors will be involved: masked monitor will perform the checks of the study evaluations and procedures and will not be involved in the drug accountability. A second one, unmasked monitor will be defined before the start of the study and will be responsible for performing the drug accountability. He/she will not be involved in any other monitoring activities. This will be done to safeguard the observer-masked of the study. Due care will be applied in order to avoid any disclosure of unmasked observer information to masked staff.
Co-monitoring visit could be performed by the sponsor if required.

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

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 authorized 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.

9.2 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 ALCOA principles (Attributable-Legible-Contemporaneous-Original-Accurate).

The clinical centers are 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 each one 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.

9.3 Applicable SOPs

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

9.4 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 to monitoring activities, audits, IEC review, and regulatory inspection.

9.5 Audits and inspections

The sponsor, any independent body 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 agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorized individuals to have access to all the study documentation.

10 ETHICAL CONSIDERATIONS

10.1 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 relevantEthics Committees and Health Authorities will be obtained before the start of the study.

Study notification to the Competent Authorities will be performed according to the current regulations.

The present clinical study will be carried out according to the general principles of "ICH Topic E6, CPMP/ICH/135/95", July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002.

10.2 Informed consent

Before being enrolled into 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 organized
- thetype of treatment
- any potential negative effects attributable to the study 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 jeopardizingtheir further course of medical treatment
- the existence of 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 section 11.3). The investigator will allow inspection of the forms by authorized representatives of the sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.

10.3 Insurance policy

An insurance cover has been issued in favor 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.

10.4 Study termination

The end of the trial is defined as the Last Visit of the Last Patient.
The study will be considered terminated at the date of the last visit of the last subject,upon completion of any follow-up procedure described in protocol. The investigator and thesponsor 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 bedocumentedappropriately.

10.5 Premature discontinuation of the trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMPs, e.g. due to:
  - Evidence of inefficacy of the IMPs,
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.
- Withdrawal of IMPs from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations. The whole trial may be terminated or suspended upon request of Health Authorities.

11 ADMINISTRATIVE PROCEDURES

11.1 Material supplied to the clinical center

Besidethe investigational products, the following study material will be supplied to the clinical center:

- final version of the study protocol
- e-CRF access (login and password) for each study member declared and involved in data entry
- copy of the investigator's brochure (IB) relative to the test investigational product
- product information for the reference investigational product
- informedconsent 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.

11.2 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 amendments will be sent to the EC and concerned Competent Authorities, according to the current regulations in the EU and Switzerland.

The amendment will be applicable only when it is approved by the concerned authorities, unless the changes consist of urgent safety measures to protect study subjects.

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

11.3 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, including ECGs etc., 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 including ECG tracing, insurance contracts, certificate of analysis of the IMP(s), 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.

11.4 Studysubjects' recruitment

Study participants will be recruited at each clinical centre among those patients attending the clinic for cataract surgery in single eye at a time. Ten to fifteenpatients should be recruited at each clinical center.

11.5 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 similar 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 authorization 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 on the CRFs during the study will be documented in an anonymous way (see section8.2). If, as an exception, it becomes necessary to identify a subject for safety or regulatory reasons, the monitor, the sponsor and the investigator will be bound to keep this information confidential.

11.6 Publication policy

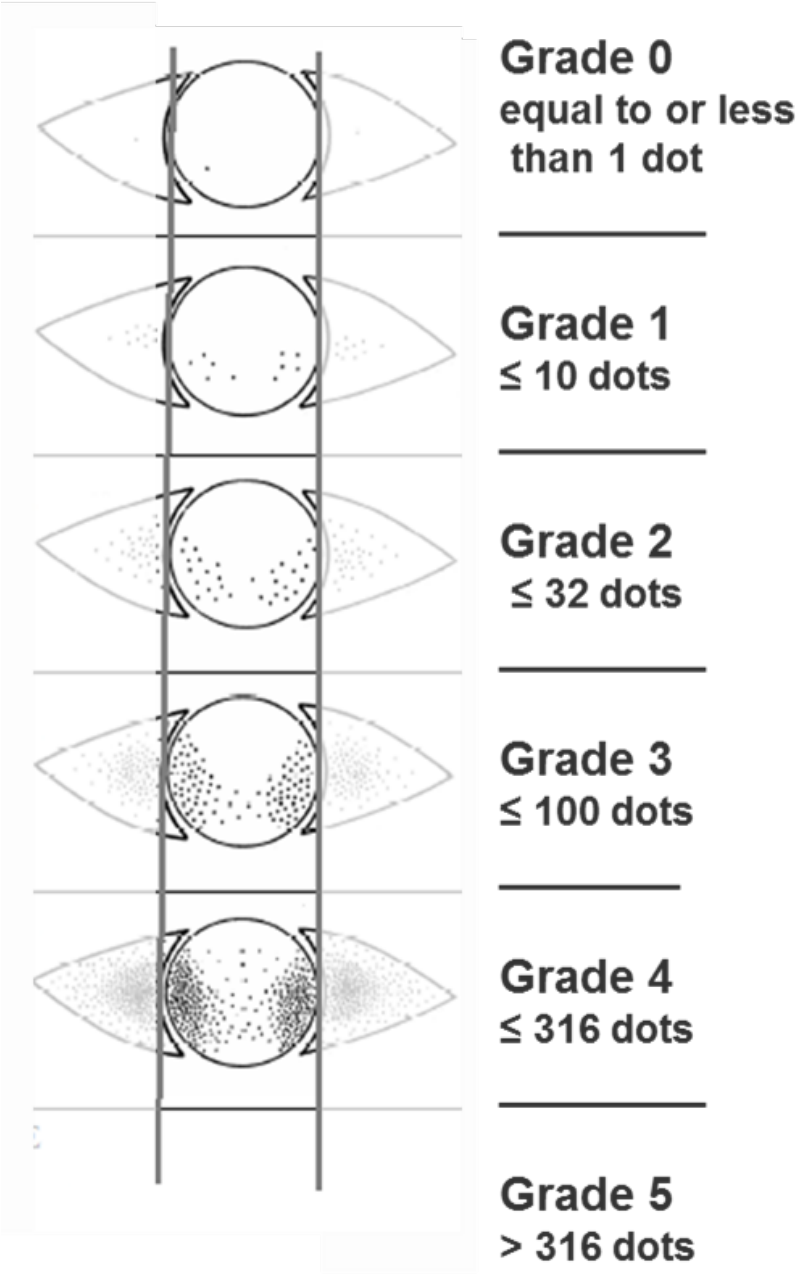
The sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public 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(s), 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(s) 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.

12 APPENDICES

12.1 Appendix 1 Oxford Scale



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