Sintetica®

CLINICAL STUDY PROTOCOL

Clinical Study Protocol Nº: CHL.3-01-2021-M
CRO Clinical Study Protocol No.: CRO-23-153

A prospective, observer-blind, randomized clinical trial to investigate and compare the clinical efficacy of Chloroprocaine 3% gel and Oxybuprocaine 0.4% eye drops anesthesia for clinical practice in pediatric population.

EU Trial Number: 2023-504477-21-01

Test product:	Chloroprocaine 3% ophthalmic gel, Sintetica S.A., Switzerland
Reference product:	Benoxinato Cloridrato 4 mg/mL eye drops (Oxybuprocaine Chlorhydrate 0.4%), ALFA INTES, Italy
Sponsor:	Sintetica S.A., Via Penate 5, CH-6850 Mendrisio, Switzerland Phone: +41.91.640.42.50; Fax: +41.91.646.85.61
Coordinating Investigator	Prof. E. Pedrotti, Clinica Oculistica dell'Azienda Ospedaliera Integrata di Verona, Policlinico di Borgo Roma (Verona), Italy
Development phase:	Phase III
Version and date:	Version 5.0 – November 10, 2023

This study will be conducted in compliance with the protocol, the Clinical Trial Regulation (EU) 536/2014 and the principles of Good Clinical Practice (GCP) [ICH topic E6 (R2)], and with the applicable EU and local regulatory requirements.

CLINICAL STUDY PROTOCOL AMENDMENT HISTORY

CSP version N.	Date issued	Description
1.0	30JUL2021	Original version
1.1	25AUG21	Final version submitted to FDA for advice
2.0	22DEC22	According to the FDA advice, the definition of successful anesthesia was modified. Accordingly, the study sample size was re-calculated and the statistical analysis methods were completed. Several sections were clarified and completed. A few typos were corrected.
3.0	03MAY23	➢ National study coordinating investigator has changed. ➢ Information about electronic consent use has been included. ➢ Conjunctival anaesthesia assessment is now foreseen for both eyes. The primary efficacy analysis will be performed on the right eye only, as already foreseen in the previous protocol version. ➢ Binocular indirect ophthalmoscopy was added beside slit lamp examination for assessment in small children, according to the Investigator's opinion. ➢ A few typos were corrected.
4.0	30AUG23	According to the MSC requests for information the following changes were made: ➢ A schematic diagram of the study design has been included ➢ The rationale for the Test IMP dose selection has been expanded ➢ The section entitled "Discussion of design" has been amended to better explain the blinding of the study participants ➢ The pregnancy test was included in Table 1 – Study schedule ➢ The complete list of contraceptive measures required, in line with CTFG recommendation on Contraception and pregnancy-2020, taking into account the characteristics of the IMPs has been included as requested ➢ The Risk/Benefit section has been expanded, as requested ➢ Concomitant therapies were further specified as suggested ➢ It has been specified that the right eye will be treated first, followed by the left eye. In the same way, the right eye will be assessed first for efficacy and safety evaluation, followed by the left eye

		➢ An additional descriptive analysis by age group has been specified
5.0	10NOV23	According to the final assessment report of the concerned RMS, the authority's requests were addressed as follows: ➢ A different comparator (reference product), which does not have contraindications in any study population age range, will be used. All related protocol parts were modified accordingly. ➢ Post-dose assessment for vital signs has been added. ➢ A few typos were corrected.

2 PROTOCOL APPROVAL

2.1 SPONSOR

SPONSOR
Sintetica S.A., Switzerland

Sergio Cantoreggi, PhD
Corporate Chief Scientific Officer

17 Nov 2023
Date


Signature

2.2 INVESTIGATOR(S)

STUDY COORDINATOR

Prof. E. Pedrotti
Clinica Oculistica dell'Azienda Ospedaliera Integrata di Verona, Policlinico di Borgo Roma (Verona), Italy

I have read this protocol and agree to conduct this study in compliance with the protocol, the Declaration of Helsinki, the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), the Clinical Trial Regulation (EU) 536/2014 and the applicable local law requirements, including supervising any individual or party to whom I will delegate trial-related duties and functions at the trial site.

28/4/23
Date


Signature

2.3 CRO

CROSS Research S.A., Switzerland

BIOSTATISTICIAN
Alessandra Gentili
Biometry Manager, Unit Head

10NOV2023 _____ Alessandra Gentili _____
Date Signature

AUTHOR OF THE CLINICAL STUDY PROTOCOL
Chiara Leuratti
Clinical Projects Unit Head and Senior Medical Writer

10 NOV 2023 _____ Chiara Leuratti _____
Date Signature

3 Contacts page for the study

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Author of Clinical Study Protocol	**Chiara Leuratti** Clinical Projects Unit Head and Senior Medical Writer CROSS Research S.A., Switzerland
All details regarding the CRO for monitoring will be presented in the Investigator's File	

4 STUDY SYNOPSIS

Study Title	A prospective, observer-blind, randomized clinical trial to investigate and compare the clinical efficacy of Chloroprocaine 3% gel and Oxybuprocaine 0.4% eye drops anesthesia for clinical practice in pediatric population.
Sponsor	Sintetica S.A.
Protocol Sponsor code	CHL.3-01-2021-M
CRO clinical study protocol N.	CRO-23-153
EU Trial Number	2023-504477-21-01
Clinical phase	Phase III
Study design	Prospective, multicenter, randomized, active-controlled, parallel-group, observer-blind, Phase III pediatric non-inferiority study
Planned Schedule	Planned initiation: Q1 2024 Planned Last Patient Last Visit (LPLV): Q3 2024
Planned n. of centers / countries	Approximately 3 centers in Italy
Indication	Local anesthesia by topical ophthalmic instillation
Test Product	Chloroprocaine 3% gel, Sintetica S.A., Switzerland
Reference product	Benoxinato Cloridrato 4 mg/mL eye drops (oxybuprocaine chlorhydrate 0.4%), ALFA INTES, Italy
Randomization	Patients will be allocated to the Test (Chloroprocaine) arm or Reference (Oxybuprocaine chlorhydrate) arm according to a 1:1 ratio
Dose regimen	The assigned investigational product (2 drops) will be instilled in both eyes of each subject. Administrations will be performed at the clinical centre by the Investigator or his/her deputy on study day 1. For each administration, the 2 drops will be instilled one at the time, at a 1 min interval. Administration will be performed as follows: 1 drop in the right eye, followed by a drop in the left eye. After 1 minute from each administration, the second drop will be administered in the right eye followed by the left eye.
Sample Size	Seventy-four (74) male/female outpatients, aged 0-17 years (18 years not completed at screening and during the study period), scheduled to undergo ocular exams with a need of ocular surface anesthesia.
Study Duration	Up to 8 days (+/-3 days) or up to 15 days (optional) duration per patient: - Inclusion visit: D -7/D1 - Follow-up: D2 (phone contact) - Final visit: D8 (+/-3 days) - Optional visit/unscheduled visit: up to D15 (on-site visit or phone contact)
Inclusion criteria	To be enrolled in this study, patients must fulfil all these inclusion criteria: 1. Age ≥ one day of life (newborn, infant, child) and 17 years included (not anticipated to turn 18 during the study). 2. Female subjects currently either of: • Non-childbearing potential (i.e., premenarchal or physiologically incapable of becoming pregnant, including any female who is surgically sterilized via documented hysterectomy or bilateral tubal ligation), or

	• Childbearing potential (i.e., postmenarchal girls): the subject is eligible to enter and participate in this study if she is not lactating, has a negative pregnancy test and agrees to abstain from intercourses or uses, until study completion, a valid contraceptive method according to CTFG recommendation on Contraception and pregnancy, v 1.2-2020, i.e.: o Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit o A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit o A male sexual partner who agrees to use a male condom with spermicide o A sterile sexual partner 3. Signed written informed consent by both parents or legal representative(s) (unless only one has legal authority). Written informed assent for adolescents aged 12-17 years included and, whenever possible, informed assent for children aged 6 to 11 years included. Ability of the subjects and their parents/legal representative(s) to understand and comply with the protocol requirements, study-specified visit schedule and procedures. 4. Scheduled to undergo a routine clinical procedure which needs local ocular surface anesthesia, including but not limited to applanation tonometry, gonioscopy, Ultrasound Biomicroscopy (UBM), ocular ultrasonography, retinal peripheral examination with blepharostat and scleral indentation.
Exclusion criteria	Patients fulfilling at the inclusion visit ONE OR MORE of the following exclusion criteria will not be enrolled in the study: ***Ophthalmic exclusion criteria*** 1. Previous ocular surgery less than 6 months before screening 2. Eye movement disorder (nystagmus) 3. History of herpetic keratitis 4. Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration, corneal damage and superficial punctuate keratitis) 5. History of ocular traumatism, infection or inflammation within the last 3 months ***Systemic/non ophthalmic exclusion criteria*** • General history: 6. Any other medical or surgical history, disorder or disease such as acute or chronic severe organic disease: hepatic, endocrine neoplasia, hematological diseases, severe psychiatric illness, cardiac rhythm disorders and/or any complicating factor or structural abnormality judged by the investigator to be incompatible with the study • Allergic history: 7. Known hypersensitivity to one of the components of the investigational products ***Exclusion criteria related to general conditions***

<table>
<tr><td></td><td>
8. Non-compliant patient and/or parent(s)/legal representative(s) (e.g., not willing to attend the follow-up visits, way of life interfering with compliance)
9. Participation in another clinical study in the last three months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
10. Already included once in this study
Exclusion criteria related to previous and concomitant medications / non-product therapies
11. 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="4">NOT ALLOWED CONCOMITANT MEDICATIONS (washout times)</td></tr>
<tr><td colspan="3">Before Inclusion</td><td>Inclusion</td></tr>
<tr><td>30 days</td><td>15 days</td><td>7 days</td><td>Day 1</td></tr>
<tr><td colspan="4">Any change in concomitant anti-depressant medication ……..</td></tr>
<tr><td colspan="4">Any topical ocular treatment ……</td></tr>
<tr><td></td><td colspan="3">Systemic opioids and morphinic drugs .....</td></tr>
<tr><td></td><td colspan="3">Sulphonamides</td></tr>
<tr><td></td><td colspan="3">Anticholinesterase drugs</td></tr>
<tr><td colspan="2"></td><td colspan="2">Any change in other systemic medication already ongoing before inclusion visit</td></tr>
<tr><td colspan="3"></td><td>Others systemic antalgics drugs (except paracetamol)</td></tr>
<tr><td colspan="3"></td><td>Silver nitrate (bactericides), Mercury salts (some disinfectants), Alkaline substances (e.g. detergents)</td></tr>
</table>
* Paracetamol after primary endpoint assessment and oral, implantable, transdermal, or injectable contraceptives for child-bearing potential girls during the entire study will be allowed
</td></tr>
<tr><td>Primary objective</td><td>The primary objective of the study is to evaluate the efficacy of Chloroprocaine 3% ophthalmic gel as compared to Oxybuprocaine chlorhydrate 0.4% eye drops anesthesia for clinical practice in pediatric population.</td></tr>
<tr><td>Secondary objective</td><td>The secondary objective of the study is to evaluate the safety of Chloroprocaine 3% ophthalmic gel as compared to Oxybuprocaine chlorhydrate 0.4% eye drops anesthesia for clinical practice in pediatric population.</td></tr>
<tr><td>Primary endpoint</td><td>Primary endpoint will be to assess the proportion of patients in each treatment group with a successful conjunctiva anesthesia <u>in the right eye</u>, 5 minutes after study product administration, i.e. right before the ocular examination, to be assessed by eye spear sponge.
A successful conjunctiva anesthesia is defined as ocular discomfort equal to 0 (=no hurt) on the Wong-Baker faces pain rating scale (WBFPS) for patients equal to or older than 3 years old.
For patients less than 3 years old, a successful conjunctiva anesthesia is defined as ocular discomfort equal to 0 (= relaxed and comfortable) as per the Faces, Legs, Activity, Cry, Consolability scale (FLACC).
Note: Conjunctival anaesthesia will be assessed in both eyes, but primary assessment will be the one performed on the right eye, as specified above</td></tr>
<tr><td>Secondary endpoints</td><td>Safety endpoints:
- Objective ocular signs (palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, follico-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells, flare) and other objective ocular signs,</td></tr>
</table>

	assessed by slit lamp examination (SLE) or binocular indirect ophthalmoscopy (BIO), will be graded according to the following scale: 0=none, 1=mild, 2=moderate, 3=severe. Timepoints: D1 before and after IMP administration, D8 and if needed at the unscheduled visit up to D15. - Adverse events occurrence throughout the study - Product global tolerance will be graded by the Investigator by answering the following question "How do you consider the study product global tolerance" using the following scale: 0=very unsatisfactory, 1=unsatisfactory, 2= satisfactory, 3=very satisfactory. Timepoint: D1 post-dose
Study Procedures	The study will include an Inclusion visit (Day -7/Day 1), a Follow-up visit (Day 2, phone visit), a Final visit (Day 8± 3 days) and an Optional/Unscheduled visit, if applicable (up to day 15). In case of premature discontinuation, as far as possible, an early termination visit (ETV), involving the same procedures/activities of the final visit, will be performed. **<u>Visit 1: Inclusion visit (Day -7 to Day 1)</u>** Patients scheduled to undergo an ocular examination in one eye or both eyes (e.g. tonometry) will be informed about the aims, procedures and possible risks of the study and will be asked to sign the informed consent form (parents/legal representative) and informed assent, as applicable, for the inclusion in the trial up to 7 days before the visit. On Day 1, the study inclusion/exclusion criteria will be verified. Blood pressure, heart rate, AEs occurrence will be assessed. Patients will be randomized to either chloroprocaine 3% gel (Test) or oxybuprocaine 0.4% eye drop (Reference) treatment group and the allocated treatment will be administered by instillation in both eyes. Efficacy (conjunctival anesthesia assessment with an eye spear sponge, just before the scheduled diagnostic examination) and safety endpoints (SLE/BIO) will be assessed in both eyes. Product global tolerance will be graded by the Investigator and vital signs post-dose will be measured (see table 1- study schedule). For all assessments, the right eye will be evaluated first followed by the left eye. *Note: Informed consent form and assent form can be signed, as applicable, within 7 days before inclusion visit. All other procedures must be done at D1.* **<u>Visit 2: Follow-up phone visit (Day 2)</u>** The phone call will be made by a blinded investigator. ➢ Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments. ➢ AEs occurrence (see table 1- study schedule). **<u>Visit 3: Final visit (Day 8 ± 3 days)</u>** The procedures will be carried out by a blinded investigator. ➢ Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments. ➢ AEs occurrence. ➢ SLE/BIO in both eyes (right eye first, followed by left eye). (see table 1- study schedule). If it is needed as per investigator's judgement, a final follow-up with the same procedures will be performed up to D15 (see table 1- study schedule – and below).

	Optional visit/Unscheduled visit – phone call or on-site visit – (Visit 4, up to Day 15 as per Investigator's judgement) ➢ Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments. ➢ AEs occurrence. ➢ SLE/BIO in both eyes (on-site visit only) (right eye first, followed by left eye). (see table 1- study schedule).
Definition of analysis sets	Safety set: All patients who received at least a fraction of the dose of the investigational product. Intention-to-treat (ITT): all randomized patients. Per Protocol Set (PPS): all randomized patients who received the treatment without any major deviation from the protocol. The exclusion of patients from the analysis sets will be discussed during a blind review meeting that will be held before database lock and complete unblinding. Subjects will be evaluated according to the treatment they were assigned to for the efficacy analysis (ITT, PPS) and according to the treatment they actually receive in the Safety set. Data analysis for primary efficacy outcome will be performed on the ITT set. A sensitivity analysis on the PP Set will also be performed for the primary endpoint. Safety parameters will be analyzed on the Safety set.
Statistical analysis	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. The primary endpoint of the study is defined as the proportion of subjects in each treatment group with a successful surface anesthesia (right eye), i.e., score 0 on the WBFPS for children aged ≥ 3 years and score 0 on the FLACC scale for children aged < 3 years, determined 5 minutes after study product administration, i.e., right before the ocular examination. Conjunctival anaesthesia scores for the right eye (study eye) and for the left eye (non-study eye) will be listed by subjects and summarized by frequency and descriptive statistics overall (i.e. for the 0-3 and 3-17 years age groups together) and by age group (corresponding to the two different scales). The primary analysis will be performed on the ITT set. A non-inferiority test will be used to compare the proportion of success in each treatment group. The difference in proportions and its one-sided 95% confidence interval will be derived from the SAS FREQ procedure using RISKDIFF option and specifying the NONINFERIORITY (or NONINF) to request the Farrington-Manning score test for noninferiority. The significance of the test and therefore the non-inferiority of the Test versus the Reference product will be confirmed if the lower limit of the 95% confidence interval is greater than the noninferiority margin (-0.25). A sensitivity analysis will be done on the PP set, using the same methodology applied for the ITT set.

	According to the EMA addendum to ICH E9(R1) about estimands and sensitivity analysis (ICH E9 (R1). EMA/CHMP/ICH/436221/2017 17 February 2020), the primary efficacy analysis will be conducted under a "Treatment policy strategy". Under the treatment policy strategy, if an intercurrent event has occurred or not is irrelevant, the data will be collected and analyzed regardless. For example, if a patient took rescue medication, or discontinued from the trial, the data post the event would be included in the analyses. This policy reflects the intention-to-treat (ITT) principle. Indeed, in this trial, in the case of unsuccessful anesthesia requiring the use of rescue anesthesia to proceed with the diagnostic procedure, the patients will be regarded as failure due to a score greater than 0. If the primary efficacy parameter cannot be collected due to complications preventing the assessment of anesthesia success, a "composite strategy" for the handling of missing data will be used and the patient will be regarded as failure.

TABLE 1. – STUDY SCHEDULE

Study procedures	**Visit 1 Inclusion visit D-7/D1***	**Visit 2 Follow-up visit D2 (phone visit)**	**Visit 3 Final visit D8 (+/-3 days)**	**Unscheduled visit (Visit 4) up to D15 (if needed as per investigator's judgement)**
Information on the study and Informed consent/assent signature (as applicable)	X			
Demography*****	X			
Ocular medical and surgical history*****	X			
Systemic medical and surgical history*****	X			
Previous and concomitant ocular and non-ocular treatments	X	X	X	X
Pregnancy test (postmenarchal girls only)*****	X			
Slit lamp examination/Binocular indirect ophthalmoscopy	X**		X	X***
Adverse events	X	X	X	X
Verification of inclusion and exclusion criteria / Status of the patient	X			
Allocated treatment group	X			
IMP administration (2 drops in each eye)	X			
Vital signs******	X			
Efficacy assessment (conjunctival anaesthesia)****	X			
Product global tolerance	X (Day 1, post-dose)			

**Informed consent form and assent form can be signed, as applicable, within 7 days before inclusion visit as per local practice. All other procedures must be done at D1.*

***Before (0 min) and after (60 min) the instillation (Before instillation to check patient's eligibility and after instillation to assess the safety)*

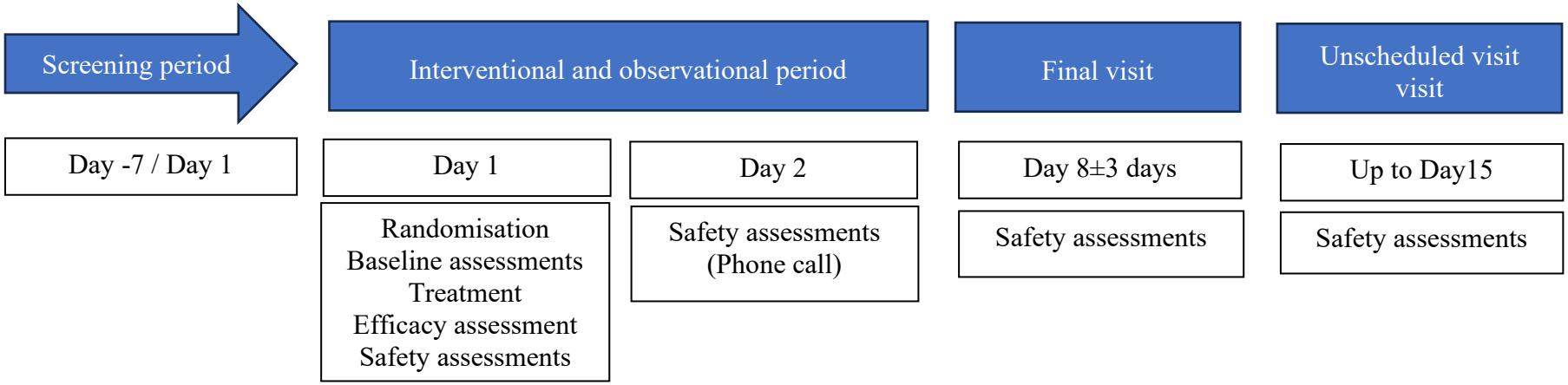
****Only if the visit is on-site*

*****Both eyes. Five (5) min after study product administration, i.e., right before the ocular examination (Day 1). WBFPS for patients ≥ 3 years or FLACC scale for patients <3*

******At screening only*

******* At screening and post-dose*

TABLE 2. – SCHEMATIC DIAGRAM OF STUDY DESIGN



5 TABLE OF CONTENTS

6 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	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CTFG	Clinical Trials Facilitation and Coordination Group
CRS	Clinical Study Report
CV	Coefficient of Variation
D	Day
DBP	Diastolic Blood Pressure
EC	Ethics Committee
eCRF	Electronic Case Report Form
ETV	Early Termination Visit
FLACC	Face, Legs, Activity, Crying and Consolability scale
FPFV	First Patient 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	Investigational Medicinal Product
ITT	Intention To Treat
IV	Intravenous
LPLV	Last Patient Last Visit
LA	Local Anaesthesia
MAH	Marketing Authorization Holder
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MF	Missing as Failure
MI	Multiple Imputation
NA	Not Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PK	Pharmacokinetics
PNB	Peripheral Nerve Block
PP	Per Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse 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
WBPS	Wong-Baker faces pain rating scale
WC	Worst Case
WHODDE	World Health Organization Drug Dictionary Enhanced

7 INTRODUCTION

7.1 Background

Topical local anaesthetics (LAs) play an important role in the practice of ophthalmology, especially for less invasive outpatient surgeries and routine examinations that require contact onto the ocular surface.
Anaesthetics topically applied to the eye act directly on the corneal epithelium and stroma, with a duration of effect up to 15–20 minutes depending on the properties of the drug used. Their safety profile is generally considered acceptable, especially in occasional use (1).

Current practices for ocular topical anaesthesia include oxybuprocaine (in Europe), proparacaine (in US) or tetracaine (both in EU and US) used as eyedrops. Importantly, during recent years there has been an increase in the off-label use of lidocaine 2% gel for ophthalmic procedures (2, 3). The majority of these reports highlighted favorable patient-pain profiles with the use of viscous preparation as the sole anaesthetic agent. This led to the 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 (4).
Although many adult ocular procedures may be performed equally well under local or general anesthesia, with children, the anesthesiologist almost always must administer general anesthesia to guarantee satisfactory surgical conditions. Moreover, in routine clinical practice with children, it may be difficult to perform tests that require touching the ocular surface. As strategies may be used to divert infants' attention during the examination, and teenagers can frequently be persuaded to go along with the examination, children between these two age groups can be nearly impossible to examine and often require general anesthesia.

Considering a gel formulation as potentially more effective than usual drops used for topical anesthaesia (5), we aim at demonstrating the benefits of a chloroprocaine 3% gel in children undertaking routine clinical examinations such as applanation tonometry, gonioscopy, retinal peripheral examination with blepharostat and scleral indentation, and ultrasound imaging (ocular ultrasonography and ultrasound biomicroscopy).

7.1.1 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.

7.1.2 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 has been present on the Swiss market for local anaesthesia by infiltration, for Peripheral Nerve Block (PNB) and for epidural block.
In 2020, the Extension Application of the existing MA of Ampres 10 mg/mL was granted in Europe, by introducing a new strength (Ampres 20 mg/mL), a new route of administration (perineural injection) and a new indication (perineural anaesthesia for short-duration surgeries, not exceeding 60 minutes).

Thanks to very favourable pharmacokinetic (PK) characteristics, chloroprocaine is currently considered the local anaesthetic with the safest toxicological profile.

Sintetica S.A. has previously conducted a phase I/II, a phase II/III and a phase III clinical trial for Chloroprocaine Hydrochloride ophthalmic gel 3% (30 mg/mL) intended for ocular surface anesthesia during ophthalmologic procedures in adults. The phase I/II and phase II/III efficacy, safety and local tolerability study determined that chloroprocaine gel was overall well tolerated with an optimal profile of efficacy, while the larger phase III efficacy and safety study proved the efficacy of chloroprocaine for surface anesthesia during ophthalmologic procedures (cataract surgery) in comparison with tetracaine.
Totally, more than 300 subjects (patients and healthy volunteers) have been exposed to Chloroprocaine Hydrochloride ophthalmic gel 3%.

Moreover, Sintetica 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 patients in total. Moreover, another pediatric study assessing the efficacy and safety of chloroprocaine 1% and 2% for PNB is currently ongoing.
Chloroprocaine proved to be highly efficacious in all the above-mentioned clinical trials, and its very favourable safety profile has been strongly confirmed.

Chloroprocaine 3% proved to be efficacious and well tolerated also in the full package of preclinical studies introduced in section "Non-clinical background information" of this protocol. 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 in liquid and in jelly formulation (6).
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.

7.1.3 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 (7).

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 (8).

The drug product is topically applied to the cornea. There is little or no measurable systemic absorption.

7.1.4 Pharmacokinetics

Chloroprocaine onset of action is rapid (usually within very few minutes) and the duration of its action is short, (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)(9).

7.1.5 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 (10).

7.1.6 Clinical efficacy

Similar 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 the literature and 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 procedures and short surgeries, matching the important key benefits required for a local anaesthetic of choice in this setting.

In a Phase I/II clinical study (12) conducted in healthy adult male and female volunteers administered a single dose of chloroprocaine 3% ocular gel as ocular anesthetic, the proportion of subjects who achieved anesthesia of the treated eye at 5 min after instillation

was 89.7%. The median time to anaesthesia was 0.67 min (i.e., 40 sec). Mean value was 2.41 min (95% CI: 1.89, 2.92).
A double-masked, vehicle-controlled, phase II/III study conducted in healthy volunteers (13) showed that successful anaesthesia in the chloroprocaine 3% gel group was achieved by 95% of subjects vs. 20% of subjects in the control group. Median time to anaesthesia onset with chloroprocaine 3% was 0.67 min. Anaesthesia in the active treatment group lasted for a median (min, max) time of 19.3 min.

In a previous Phase III study conducted on 338 adult patients scheduled for cataract surgery and treated with either chloroprocaine 3% gel or tetracaine 0.5% eye drops as topical anesthetics (14), the proportion of patients with a successful surface anesthesia (defined as score 0=no pain/discomfort plus score 1=occasional pressure sensation), without any supplementation just before intraocular lens implantation (T4 ; primary endpoint) was 92.0% and 90.5% in the Test and Reference treatment group, respectively.

7.1.7 Clinical safety

The general overview of the safety profile of chloroprocaine comes from a 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 favorable 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 the product is cleared efficiently even in former preterm neonates also when receiving high epidural infusion rates (5, 11). Rapid plasma degradation, rapid onset, lack of accumulation, makes chloroprocaine systemic toxicity less likely compared to other amide-type LAs (2). Importantly, chloroprocaine is considered the local anaesthetic with the safest toxicological profile compared to other LAs, with a very low risk 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 endpoints in a phase 2 study, to confirm low systemic exposure to chloroprocaine following intrathecal administration, the most sensitive model to assess 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 and its well-known safety profile. Indeed, even after administration via spinal route, the drug metabolite ACBA was 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.

Considering pooled data from the clinical Phase I/II study (CHL.3-01-2020; ref. 12), Phase II/III (CHL.3-02-2019; ref. 13) and Phase III study (CHL.3/01-2019/M; ref 14), AEs were reported for 26.8% of the 317 subjects exposed to chloroprocaine HCl 3% ophthalmic gel, overall. The most common treatment-emergent AEs were eye disorders, and in particular mydriasis (12.3%), followed by conjunctival hyperemia (5%), eye irritation (2.8%), punctate keratitis (2.2%), conjunctival haemorrhage (1.9%) and corneal edema (1.6%).
However, mydriasis was recorded only in the Phase I/II and Phase II/III studies. In fact, in the Phase 3 study, mydriasis was not reported as an AE because according to the clinical practice in cataract surgery, a mydriatic product was also administered as allowed concomitant medication before surgery.
The AEs reported in the 3 cited clinical trials did not give rise to any safety concerns.

Also post marketing data strongly confirms the favorable safety profile of chloroprocaine as local anaesthetic (LA). 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 on different factors, such as indication and patient's characteristics. Nonetheless calculation of exposure is based upon estimated 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 new safety concerns have been identified in relation to the drug product and its safety profile.

7.2 Risks and benefits

The Test IMP evaluated in the present study is marketed in the US, under the brand name of IHEEZO™ for topical ophthalmic use, indicated for ocular surface anaesthesia in adults.

Benoxinato Cloridrato INTES 4 mg/mL (oxybuprocaine chlorhydrate 0.4%) eye drops is marketed in Italy and is commonly used for ocular surface anaesthesia in adults and children of all ages, without restrictions, for the same indication, i.e. ocular surface anesthesia.

Possible severe side-effects related to the two investigational products may be caused or increased due to the following factors:

- Subject factors: condition of the ocular surface, certain medical conditions, certain medications.
- Practitioner factors: training, years of experience, number of procedures performed.

To avoid these side-effect factors, the following conditions are foreseen:

- Subjects have to meet very specific inclusion/non-inclusion criteria before entering the clinical trial (see § 10.2 and § 10.3).
- The Investigators participating in this clinical trial are trained and experienced practitioners in the field of paediatric ophthalmology.

The most common adverse reactions that have been reported in the 2 placebo-controlled clinical trials in adult patients (see § 7.1.6 and § 7.1.7) with the Test product (chloroprocaine hydrochloride 3% eye gel) were mydriasis, followed by conjunctival hyperemia and eye irritation (Iheezo™; Highlights of Prescribing Information). These events were transient and resolved by study end or by the study follow-up.

Other undesirable effects that could possibly occur would be local intolerance effects (e.g., mild burning, blurred vision). These effects cannot be totally excluded when applying a topical ocular product, even if not previously reported.

Reported adverse events after administration of the Reference product were mainly occasional and transitory local irritation events, e.g., burning sensation, pain and conjunctival hyperemia. Allergic sensibilization could occur, but only after repeated doses.
Following oxybuprocaine absorption through damaged mucosae or the skin, nausea, vomiting, nervous system excitation phenomena, pallor, sweating, somnolence, hypotension, arrhythmia (very rarely), respiratory insufficiency and methemoglobinemia (very rarely) have occasionally been observed. In addition, the Reference product contains potassium dihydrogen phosphate as an excipient, which could very rarely cause opaque spots on the cornea (due to calcium accumulation) during prolonged treatment in patients with severe corneal damage of the cornea. However, in the present study healthy volunteers with intact cornea are included and the product is administered as a single dose.
Accidental overdosing of either product is excluded considering that instillations will be performed by very experienced practitioners.

Considering that the products are topical ocular products administered by instillation and that plasma exposure is negligible, no systemic effects are expected.

Adverse events following investigational products topical instillation in the eyes of the study paediatric population cannot be ruled out, but, based on the experience with oxybuprocaine chlorohydrate 0.4%, the side effects are expected to be similar to those reported in the adult population for both Test and Reference product.

Expected benefits of the Test investigational product (chloroprocaine 3% 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 higher local exposure 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.

Considering the information above, the benefit/risk ratio of this clinical trial appears to be favorable.

7.3 Study rationale

A chloroprocaine gel formulation may represent an improved product that could lead to better anaesthesia. Chloroprocaine can be considered as the ideal anaesthetic for local anaesthesia in patients undergoing ocular exams, 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. The formulation was investigated in the 3 previous clinical studies in adults (11-13) demonstrating a very good safety profile and efficacy similar to that of the Reference products.

According to FDA request and following scientific advice with the Authority, Sintetica now intends to perform a phase 3 study on pediatric patients undergoing ocular exams to assess the safety and efficacy of topical anaesthesia using chloroprocaine 3% gel.

This prospective, observer-blind, randomized, controlled, non-inferiority phase 3 study will be conducted in approximately 3 sites in Italy. We consider that neither intrinsic ethnic factors such as race, genetic polymorphisms and genetic diseases, nor extrinsic ethnic factors such as culture, socio-economic 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.

8 STUDY OBJECTIVES

8.1 Primary objective

The primary objective of the study is to evaluate the efficacy of Chloroprocaine 3% ophthalmic gel as compared to Oxybuprocaine chlorhydrate 0.4% eye drops anesthesia for clinical practice in pediatric population.

8.2 Secondary objective

The secondary objective of the study is to evaluate the safety of Chloroprocaine 3% ophthalmic gel as compared to Oxybuprocaine chlorhydrate 0.4% eye drops anesthesia for clinical practice in pediatric population.

9 INVESTIGATIONAL PLAN

9.1 Overall study design

This will be a prospective, multicenter, randomized, active-controlled, parallel-group, observer-blind, Phase III non-inferiority study.

The first patient first visit (FPFV) is defined as the 1st visit performed at the clinical center by the 1st screened patient (1st signed informed consent/assent).
The last patient last visit (LPLV) is defined as the last visit performed by the last patient, i.e., the last visit foreseen by the study protocol, independently of the fact that the patient is a completer or a withdrawn patient.

9.2 Visit schedule:

- Inclusion visit (Visit 1: Day-7 / Day 1),
- Follow-up visit (Visit 2: Day 2, phone visit),
- Final visit (Visit 3: Day 8±3 days)
- Optional visit/Unscheduled visit - phone call or on-site visit (Visit 4: up to Day 15)

9.3 Discussion of design

The study has been designed to assess the non-inferiority of chloroprocaine 3% ophthalmic gel (Test) versus Benoxinato Cloridrato 4 mg/mL (oxybuprocaine chlorhydrate 0.4%) eye drop solution (Reference) in eye surface anesthesia in children undergoing ocular exams.

As also reported in § 7.3, the study was designed in line with a request from FDA and following a scientific advice with the Authority.

In designing the study, the following guidelines were taken into consideration: ICH E9 and ICH E9(R1) Guideline on Statistical principles for clinical trials (28, 29); the Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99; 30); and the Points to consider on switching between superiority and non-inferiority guideline (CPMP/EWP/482/99; 31).
Considerations on proposed success rate and the statistical test non-inferiority margin for the study are given in § 13.3.

With regards to anesthesia, topical anesthesia has become the most common form for routine practice. In this study, each patient will be allocated to a treatment arm (chloroprocaine 3% ophthalmic gel or oxybuprocaine chlorhydrate 0.4% eye drop solution) according to a computer-generated randomization list. Patients in both groups will receive two drops in each eye of the assigned study products before ocular exam.

The study will be observer-blind: an independent blind investigator will perform the study assessments, i.e., will assess the primary endpoint (successful conjunctival anesthesia) at D1 together with the patient when applicable, i.e., for patients ≥3 years old, and all safety endpoints.

Considering that the study participants will also assess treatment efficacy in terms of pain/discomfort (see § 12.2.1.1) and for this reason will act as "observers", also the patients will be blinded with respect to the received treatment.

Another staff member, in open conditions, will be in charge of product instillation.

The dose of chloroprocaine 3% ophthalmic gel was selected taking into consideration the following:
The Test investigational product for this study, i.e. IHEEZO™ 3% (chloroprocaine hydrochloride) ophthalmic gel is authorized in the United States for ocular surface anesthesia in adults. The recommended dose of IHEEZO™ is 3 drops applied topically to the ocular surface in the area of the planned procedure. IHEEZO™ may then be reapplied as needed to maintain the anesthetic effect. The 3 drops are administered at a 1 min interval, according to the posology applied in the clinical trials performed for the clinical development of the test product.
According to the present CSP, the IMP paediatric dose will be 2 drops to be instilled in both eyes of each subject, at a 1 min interval. Administration will be performed as follows: 1 drop in the right eye, followed by a drop in the left eye. After 1 minute from each administration, the second drop will be administered in the right eye followed by the left eye.

The test IMP dose for this study has been selected considering:

- The favourable safety profile of the IMP, supported by:
  - The extremely safe profile of the IMP, as shown in adult clinical studies program after administration of a three drops regimen which resulted in good local tolerability.
  - The unlikely systemic absorption of chloroprocaine after ophthalmic gel administration thanks to formulation properties and the high penetration of the local anaesthetic from the gel preparation into the corneal epithelia as demonstrated in local ocular pharmacokinetics studies in rabbits treated with Chloroprocaine Hydrochloride ophthalmic gel 3%.
  - The very short half-life of chloroprocaine demonstrated in the dose-finding, safety and PK Phase 2 study conducted by the Sponsor in the context of spinal anesthesia.
  - The single use administration which prevents possible accumulation of the drug in the corneal epithelium.
  - The safety margin of the proposed dose when compared to the well known toxicity profile of chloroprocaine.
- The effective dose required to provide a good anaesthesia, supported by:
  - Efficacy profile of the IMP demonstrated in adult clinical studies program, showing the rapid onset of the clinical effect and the good duration of anaesthetic effect.
  - The wide therapeutic window of topical 2-chloroprocaine.
  - The history of use and dosing of ophthalmic local anaesthetics in the paediatric population.

- Technical aspects related to the paediatric formulation:
  - The size of eyes and conjunctival sac in paediatric patients, especially in the infant population, as well as the area of contact between the posterior conjunctiva and the eye globe in children.
  - The properties of the gel formulation, which result in extended contact with the cornea.

Benoxinato Cloridrato 4 mg/mL eye drops (oxybuprocaine chlorhydrate 0.4%) was chosen as Reference product for the study because commonly used for this indication in clinical practice in Italy, also in children.

For the study, the Wong-Baker faces pain rating scale (WBFPS) and the Faces, Legs, Activity, Cry, Consolability (FLACC) scale were chosen for children aged ≥ 3 years and < 3 years, respectively. The WBFPS scale is one of the most widely used scales for pain reporting in children aged 3-18 years (14-18). It has adequate psychometric properties (14, 19), and it's easy and quick to use (20, 21). The FLACC scale is one of the most well-known and widely recommended observational pain measurement scales, frequently used for smaller children (22, 23).

Conjunctival anaesthesia will be assessed in both eyes. Results obtained on the right eye (study eye) will be the primary efficacy outcome and will be analysed as specified in § 9.4.1, results obtained on the left eye (non-study eye) will be listed and analysed descriptively.

9.4 Study endpoints

9.4.1 Primary endpoint

The primary endpoint is the proportion of patients in each treatment group with a successful conjunctival anesthesia in the right eye (study eye), 5 minutes after IMP administration, i.e., right before ocular examination, assessed by eye spear sponge. Conjunctival anaesthesia will also be assessed in the left eye (non-study eye).
The eye spear sponge (Figure 1) was suggested as the best tool for assessing conjunctival anesthesia since it is used in the pediatric population as per common daily practice and deemed the most ethical tool for dealing with such sensitive population as the pediatric one.

Figure 1 – Eye Spear Sponge

For patients aged equal to and more than 3 years old until 18 years old not completed, a successful conjunctiva anesthesia is defined as ocular discomfort equal to 0 (=no hurt) on the WBFPS, shown in Figure 2 below.

Figure 2 - Wong-Baker faces pain rating scale (WBFPS)

For patients less than 3 years old, a successful conjunctiva anesthesia is defined as ocular discomfort equal to an overall score of 0 (= relaxed and comfortable) on the FLACC scale (see tables below).

Face		
0 - No particular expression or smile	1 - Occasional grimace or frown, withdrawn, disinterested	2 - Frequent to constant frown, clenched jaw, quivering chin
Legs		
0 - Normal position or relaxed	1 - Uneasy, restless, tense	2 - Kicking or legs drawn up
Activity		
0 - Lying quietly, normal position, moves easily	1 - Squirming, shifting back/forth, tense	2 - Arched, rigid, or jerking
Cry		
0 - No cry, awake or asleep	1 - Moans or whimpers, occasional complaint	2 - Crying steadily, screams or sobs, frequent complaints
Consolability		
0 - Content, relaxed	1 - Reassured by occasional touching, hugging, or "talking to," distractible	2 - Difficult to console or comfort

Table 1 - Faces, Legs, Activity, Cry, Consolability (FLACC) scale

The scores are interpreted as follows:

0 =	Relaxed and comfortable
1–3 =	Mild discomfort
4–6 =	Moderate pain
7–10 =	Severe pain or discomfort or both

Table 2 - FLACC scale overall scores

Anesthesia will be defined as not successful when the score is greater than 1 on either scale (WBFPS or FLACC).

9.4.2 Secondary endpoints

Ocular and systemic safety

- Objective ocular signs (Slit Lamp Examination [SLE]/Binocular Indirect Ophthalmoscopy [BIO]): palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, follico-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells and flare, and other objective ocular signs, assessed using the following scale:

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

- Adverse events occurrence throughout the study
- Product global tolerance will be graded by the Investigator by answering the following question “How do you consider the study product global tolerance” using the following scale:

  (0) = Very unsatisfactory
  (1) = Unsatisfactory
  (2) = Satisfactory
  (3) = Very satisfactory

10 STUDY POPULATION

10.1 Target population

The study population will consist of approximately 74 evaluable pediatric patients (0-17 years [18 years not completed at screening and during the study period]) who will undergo ocular exams with a need for ocular surface anaesthesia.

Routine clinical procedures that require topical anesthesia include but are not limited to:

- Applanation tonometry: after the anesthesia has been performed, the patient's head is immobilized against a headrest or against the examiner's hand. The patient's eyelids are gently spread. The measurement of intraocular pressure is carried out by gently pressing the tip of the device against the central part of the cornea for a few seconds. The exam is painless but may elicit a blink reflex if the anesthesia is not correct.

- Gonioscopy: after the anesthesia has been performed, the patient's head is immobilized, and the patient is asked to look up. The lower eyelid is gently pulled downwards, thus exposing the inferior bulbar conjunctiva. An examination contact lens is then brought against the ocular surface, centering it over the cornea, thus allowing visualization of the endocular structures and the iridocorneal angle.

- Ultrasound Biomicroscopy (UBM): this examination is usually performed while lying down. After the anesthesia has been performed, the eyelids are gently pulled apart so that a watertight cup can be inserted in-between them. The cup is then filled with sterile water so that the imaging probe can be immersed. There is no contact between the probe and the eye surface, the water creating an interface between the two.

- Ocular ultrasonography: this examination can be performed either with closed or open eyelids. However, if the examination is to be performed with the eyelids open, surface anesthesia is necessary in order to allow contact between the ultrasound probe and the ocular surface without pain for the patient.

- Retinal peripheral examination with blepharostat and scleral indentation: the exam is aimed at evaluating the peripheral retina using an adequate instrument to hold the eyelids apart (blepharostat). Scleral indentation is a technique used to examine the peripheral fundus in conjunction with binocular indirect ophthalmoscopy. This technique enhances the contrast between normal and abnormal retina and also enables stereoscopic examination of the peripheral retina.

10.2 Inclusion criteria

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

1. Age ≥ one day of life (newborn, infant, child)***** and 17 years included (not anticipated to turn 18 during the study).

   *******(Definition of newborn's age = 0-2 months old)*

2. Female subjects currently either of:

   - Non-childbearing potential (i.e., premenarchal or physiologically incapable of becoming pregnant, including any female who is surgically sterilised via documented hysterectomy or bilateral tubal ligation),

   or

   - Childbearing potential (i.e., postmenarchal girls): the subject is eligible to enter and participate in this study if she is not lactating and has a negative pregnancy test, and agrees to abstain from intercourses or uses, until study completion, a valid contraceptive method, according to CTFG recommendation on Contraception and pregnancy v 1.1-2020 (32), i.e.:
     - Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
     - A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
     - A male sexual partner who agrees to use a male condom with spermicide
     - A sterile sexual partner

3. Signed written informed consent by both parents or legal representative(s) (unless only one has legal authority). Written informed assent for adolescents aged 12-17 years included and, whenever possible, informed assent for children aged 6 to 11 years included. Ability of the subjects and their parents/legal representative(s) to understand and to comply with the protocol requirements, study-specified visit schedule and procedures.

4. Scheduled to undergo a routine clinical procedure which needs local ocular surface anesthesia, including but not limited to applanation tonometry, gonioscopy, Ultrasound Biomicroscopy (UBM), ocular ultrasonography, retinal peripheral examination with blepharostat and scleral indentation.

10.3 Exclusion criteria

Patients fulfilling ONE OR MORE of the following exclusion criteria at the inclusion visit will not be enrolled in the study:

Ophthalmic exclusion criteria

1. Previous ocular surgery less than 6 months before screening
2. Eye movement disorder (nystagmus)
3. History of herpetic keratitis
4. Corneal, epithelial, stromal or endothelial, residual or evolutionary disease (including corneal ulceration, corneal damage and superficial punctuate keratitis)
5. History of ocular traumatism, infection or inflammation within the last 3 months

Systemic/non ophthalmic exclusion criteria

- General history:

6. Any other medical or surgical history, disorder or disease such as acute or chronic severe organic disease: hepatic, endocrine neoplasia, hematological diseases, severe

psychiatric illness, cardiac rhythm disorders and/or any complicating factor or structural abnormality judged by the investigator to be incompatible with the study

- Allergic history:

7. Known hypersensitivity to one of the components of the investigational products

Exclusion criteria related to general conditions

8. Non-compliant patient and/or parent(s)/legal representative(s) (e.g., not willing to attend the follow-up visits, way of life interfering with compliance)
9. Participation in another clinical study in the last three months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
10. Already included once in this study

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

11. 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="4">NOT ALLOWED CONCOMITANT MEDICATIONS (washout times)</td></tr>
<tr><td colspan="3">Before Inclusion</td><td>Inclusion</td></tr>
<tr><td>30 days</td><td>15 days</td><td>7 days</td><td>Day 1</td></tr>
<tr><td colspan="4">Any change in concomitant anti-depressant medication ……..</td></tr>
<tr><td colspan="4">Any topical ocular treatment ……</td></tr>
<tr><td></td><td colspan="3">Systemic opioids and morphinic drugs ..... .</td></tr>
<tr><td></td><td colspan="3">Sulphonamides</td></tr>
<tr><td></td><td colspan="3">Anticholinesterase drugs</td></tr>
<tr><td colspan="2"></td><td colspan="2">Any change in other systemic medication already ongoing before inclusion visit</td></tr>
<tr><td colspan="3"></td><td>Others systemic antalgics drugs (except paracetamol)</td></tr>
<tr><td colspan="3"></td><td>Silver nitrate (bactericides), Mercury salts (some disinfectants), Alkaline substances (e.g. detergents)</td></tr>
</table>

** Paracetamol after primary endpoint assessment and oral, implantable, transdermal, or injectable contraceptives for child-bearing potential girls during the entire study will be allowed*

10.4 Withdrawal criteria

It will be documented whether or not each patient completed the clinical study. If, for a patient, 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 receive rescue anesthesia and will not be discontinued from the study.

Patients who will present complications preventing primary endpoint assessment to be performed, will be withdrawn and the standard treatment of the hospital will be applied.

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

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

Any patient or legal representative 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 eCRF.

A complete list of discontinuation criteria is presented in § 17.3 and § 17.4.

If a patient discontinues prematurely from the study after randomization, and consent is obtained, the investigator will perform all the evaluations/assessments planned at the final visit.

10.4.1 Discontinuation procedures

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

- ask the patient to undergo, as far as possible, a final medical visit (Visit 3) to examine the patient's health condition
- arrange for alternative medical care of the withdrawn patient, if necessary
- report in the source data and eCRF date and time of the investigational product administration, and date and primary reason of study discontinuation
- record in the source data and eCRF any follow-up, if the patient is withdrawn for an AE

Discontinued patients will not be replaced.

11 CLINICAL SUPPLIES

11.1 Study Treatment

11.1.1 Description of products

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

11.1.1.1 Test product

TEST (T)	
IMP	Chloroprocaine 3%
Distributor	Sintetica S.A., Switzerland
Manufacturer	Laboratoire Unither, France
Pharmaceutical form	Ophthalmic gel
Dose	2 drops
Frequency	1 drop at the time, with a one-minute interval
Administration route	Topical instillation

11.1.1.2 Reference product

REFERENCE (R)	
IMP	Benoxinato Cloridrato 4 mg/mL eye drops
Active substance	Oxybuprocaine Chlorhydrate (same as benoxinate chlorohydrate)
Distributor	ALFA INTES, industria Terapeutica Splendore S.r.l., Via F.lli Bandiera 26, 80026 Casoria (NA), Italy
Pharmaceutical form	Ophthalmic solution
Dose	2 drops
Frequency	1 drop at the time, with a one-minute interval
Administration route	Topical instillation

11.1.2 Dose regimen

Patients will be randomized to one of the two treatment groups to receive either chloroprocaine 3% gel (Test) or oxybuprocaine chlorhydrate 0.4% solution (Reference) as topical anesthetic before ocular exam, according to the randomized, parallel-group, observer-blind design of the study.

The assigned investigational product (2 drops) will be instilled in both eyes of each subject. Administrations will be performed at the clinical center by the Investigator or his/her deputy on study day 1 (D1). Administration will be performed as follows: one drop in the right eye, followed by one drop in the left eye. After 1 minute from each administration, the second drop will be administered in the right eye followed by the left eye. The 2 drops in each eye will be instilled one at the time with 1 min interval.

11.1.3 Investigational product distribution

The two investigational products will be administered by the Investigator or by his/her deputy not involved in the primary and secondary endpoints assessments. The investigational products will be exclusively used for the present clinical study and will only be administered to the patients enrolled in the study.

11.1.4 Packaging and labelling

Packaging and labelling will be carried out by an external provider according to the kit list.

All labels will be written in the local language. The content of the labelling is in accordance with the GMP specifications, according to Annex VI to the Regulation (EU) no 536/2014 on clinical trials on medicinal products for human use and local requirements.

11.1.5 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 according to the instructions present on the corresponding SmPC/patient information leaflet.

11.1.6 Drug accountability

The Test and Reference investigational products will be provided directly to the clinical sites by the Sponsor.

Each clinical site will receive a set of Test and Reference kits. Each treatment kit will be individually labelled and packaged (see § 11.1.4).

After receipt of the investigational products supply, the pharmacist or the person identified as the recipient of the investigational products supply at each study center will confirm receipt through the IWRS 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 Sponsor's written authorization) or returned to the sponsor/manufacturer (upon written authorization), after assessment of drug accountability.

11.2 Randomization

Both the kit list and the randomization list will be computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of SAS® version 9.3 (TS1M1) or higher.
The kit list will be supplied to the Supplier before subject's kit preparation.
The randomization list will be attached to the final Clinical Study Report (CSR).

The randomization number will include a unique progressive 3-digit number (i.e., 101, 102, 103 …, 201. 202, 203,… etc.), in which the first digit of the number is the clinical site identifier (i.e.: 1 for site 1, 2 for site 2 and so on) and the other two digits is the randomization number within the site. The kit number will be a unique progressive 5-digit code (i.e., K0401, K0402, K0403 …).

11.3 Treatment allocation

The subjects will be assigned to Test (chloroprocaine) arm or Reference (oxybuprocaine) arm in a 1:1 ratio according to the randomization list. The randomization numbers will be assigned to the subjects using IWRS in a progressive order. The IWRS system will assign the kit numbers to the subjects on the basis of their treatment arm (derived from the assigned randomization number) starting from the smallest available number (based on the unique progressive 4-digit kit number).

11.4 Blinding

This is an observer-blind study.

- An independent blinded investigator will evaluate successful conjunctival and corneal anesthesia (with the patient, if applicable) and safety parameters for each patient.
- The patient will be blinded.

The observer-blind design of the trial will be maintained for the entire duration of the study for the blinded investigator until database lock. However, blinded investigator and participants may be unblinded during the trial for the occurrence of a medical emergency.

Each IMP kit will be numbered according to a randomized kits list created by the appointed CRO blinded team and provided to the supplier before the start of the study. The tracking, delivery and allocation of IMP kit numbers will be handled through the IWRS system.

11.4.1 Emergency code and unmasking procedures

Unblinding of the code for specific subjects will be fully documented in the source documents, in the eCRF and in the clinical study report.
Breaking of an individual randomization code by the investigator during the study is allowed only when knowledge of the code is essential for the subject's health. In these cases, the investigator will access the individual code of the concerned subject in the integrated eCRF system, where the unblinding action will be audit trailed. The date and the reason for breaking the code will be recorded in the system.
The system will automatically email the monitor and the Sponsor any code breaking.

11.4.2 Emergency individual envelopes

The following applies only in case of online emergency unblinding failure.
Inside the envelope, the randomization code must be clearly indicated, reporting the allocated treatment.
The true randomization code will be filed in the Investigator’s study file in a sealed envelope for each subject, with the key for its identification. Copies of the emergency individual

envelopes will be sent to the pharmacovigilance representative and to the Sponsor representative (if not coinciding).

The Investigator will open only the envelope related to the concerned subject in case of emergency. Individual code breaking will be clearly reported in the subject-related eCRF and the envelope itself; the latter is sealed again.

In any case, the CRA/monitor must be informed within 24 h from code breaking.
The date and the reason for breaking the code must be recorded in the eCRF and on the envelope. All envelope sets containing the randomization code of each subject must be kept closed even after database lock. At the end of the study, all envelope sets will be sent to the Sponsor.

11.5 Other Treatments

No other drugs than the Test and Reference products will be provided for the study.
Patients included in the study will undergo medical care before and after ocular exams, according to each clinical site practice.

12 STUDY CONDUCT

The study procedures and their schedule are summarized in Table 1.

12.1 Study visits

The study protocol foresees one study treatment for each patient. Maximum study duration will be 8±3 days (from D1 to D8) plus the screening phase (Inclusion visit) and the optional unscheduled visit up to D15.

In details, the study will include an Inclusion visit (Day -7/Day 1), a Follow-up visit (Day 2, phone visit), a Final visit (Day 8± 3 days) and an Optional/Unscheduled visit (up to Day 15). In case of premature discontinuation, as far as possible, an early termination visit (ETV), involving the same procedures/activities of the final visit, will be performed.

- **Visit 1: Inclusion Visit (Day-7[1]to Day 1)**

The procedures will be conducted by the blinded investigator, except for product preparation and administration which will be performed by another appointed member of staff in open conditions.

- Patient and patient's parents/legal representative(s) information about the aims, procedures and possible risks of the study and signature of the informed consent form/assent form (when applicable) before any study related procedures

  Patient assent and written informed consent by his/her parents/legal representative(s) (mother and father, or tutor(s)) can be signed within 7 days before inclusion visit as per local practice. All other procedures must be done at D1.
- Recording of demography data
- Ocular and systemic medical and surgical histories
- Previous and concomitant ocular and non-ocular treatments
- Vital signs (blood pressure and heart rate) at screening
- Pregnancy test for post-menarchal girls only
- Slit lamp examination/Binocular indirect ophthalmoscopy before instillation (pre-dose; 0 min) – both eyes
- Verification of the study inclusion/exclusion criteria
- Patient's allocation to one treatment group (chloroprocaine 3% gel (Test) or oxybuprocaine chlorhydrate 0.4% solution (Reference)
- Assigned product administration by instillation (2 drops in each eye) – both eyes
- Slit lamp examination/Binocular indirect ophthalmoscopy after instillation (60 min post-dose) – both eyes

[1] Informed consent form and assent form can be signed, as applicable, within 7 days before inclusion visit. All other procedures must be done at D1

- Efficacy assessment - conjunctival anesthesia assessment with an eye spear sponge (just before the scheduled diagnostic examination) – both eyes
- Vital signs (blood pressure and heart rate) post-dose
- AEs occurrence
- Product global tolerance – post-dose – both eyes

The instillation of the product will be done by appointed unblinded staff member(s) in order to maintain the blind.

- **Visit 2: Follow-up phone visit (Day 2)**

The phone call will be done by a blinded investigator.

- Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments
- AEs occurrence

- **Visit 3: Final Visit (Day 8 ± 3 days)**

The procedures will be carried out by a blinded investigator.

- Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments
- Slit lamp examination/Binocular indirect ophthalmoscopy – both eyes
- AEs occurrence

- **Optional visit/Unscheduled visit - phone call or on-site visit - (Visit 4, up to Day 15 as per Investigator's judgement)**

In case of on-site visit, the following procedures will be carried out by a blinded investigator:

- Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments
- Slit lamp examination/Binocular indirect ophthalmoscopy – both eyes
- AEs occurrence

In case of phone call, a blinded investigator will question the patient/legal representative about:

- Patient's or parents/legal representative(s) questioning about concomitant ocular and non-ocular treatments
- AEs occurrence

12.2 Study procedures

12.2.1 Efficacy measures

12.2.1.1 Conjunctival anesthesia assessment

For the assessments, the right eye will always be evaluated first, followed by the left eye.

For patients aged ≥3 up to 17 years included, the WBFPS will be used for the evaluation of conjunctiva anesthesia (see §9.4.1, Figure 2).
The patient will be asked to have the eye look up and the investigator with an eye spear sponge (see §9.4.1, Figure 1) will touch the left and the right lower conjunctiva of the eye. Both eyes will be assessed.

- The discomfort of the patient will be assessed using the WBFPS, as detailed at § 9.4.1, with the following scores:
    - 0: No hurt
    - 2: Hurts little bit
    - 4: Hurts little more
    - 6: Hurts even more
    - 8: Hurts whole lot
    - 10: Hurts worst

  The score will be reported in the individual CRF for both eyes.
  Based on the aforementioned scale, successful conjunctival anesthesia (right eye) is defined as no hurt (scale score=0) 5 min after study product administration, i.e., right before the ocular examination.

- For patients less than 3 years old, the discomfort of the patient will be evaluated using the FLACC rating scale and giving the final score as follows (see also § 9.4.1):
    - 0: Relaxed and comfortable
    - 1-3: Mild discomfort
    - 4-6: Moderate pain
    - 7-10: Severe pain or discomfort or both

  The score will be reported in the individual CRF for both eyes.
  Based on the aforementioned scale, successful conjunctival anesthesia (right eye) is defined as relaxed and comfortable (scale score=0) 5 min after study product administration, i.e. right before the ocular examination.

12.2.2 Safety measures

For the ocular assessments, the right eye will always be evaluated first, followed by the left eye.

12.2.2.1 Objective ocular signs (SLE/BIO) – Both eyes

- Objective ocular signs (Slit Lamp Examination/Binocular Indirect Ophthalmoscopy): palpebral edema, chemosis, conjunctival hyperemia, conjunctival discharge, folliculo-papillary conjunctivitis, corneal staining punctuations, anterior chamber cells, flare, and other objective ocular signs. Each sign for each eye will be evaluated using the following scale:

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

This assessment will be performed at D1, pre-dose (0 min) and after IMP instillation (60 min post-dose), at D8 and if applicable at D15.

12.2.2.2 Slit lamp examination/Binocular indirect ophthalmoscopy for additional assessments – both eyes

These assessments will be additional to the ocular symptoms assessment by SLE/BIO, and results of this assessment will not be part of the secondary endpoints.

The following ocular signs will be evaluated at the slit lamp examination or by binocular indirect ophthalmoscopy on a 0-3 scale, in addition to the SLE/BIO described at § 12.2.2.1:

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

This assessment will be performed at D1 (pre-dose and post-dose) and D8, or other time-points as applicable.

12.2.2.3 Vital signs measurements

Vital signs (blood pressure and heart rate) will be assessed at Visit 1, at screening and post-dose.

12.2.2.4 Product global tolerability assessment – both eyes

Product global tolerability will be assessed for each eye by the blinded Investigator by answering the question “How do you consider the study product global tolerance?”, using the following score scale:

(0) = Very unsatisfactory
(1) = Unsatisfactory
(2) = Satisfactory

(3) = Very satisfactory

This assessment will be performed at D1 post-dose.

12.2.2.5 Adverse events

Adverse events will be assessed throughout the study. Please refer to § 16.

12.3 Description of procedures for telephonic follow-up

On Day 2 (and possibly up to D15 for the unscheduled visit), the blinded Investigator or a deputy, 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 product instillation, 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.

13 STATISTICAL METHODS

The data documented in this trial and the measured clinical parameters will be presented using classic descriptive statistics (i.e., total number of subjects treated [N], number of observations [n], mean standard deviation [SD], minimum [Min], median, maximum [Max]) for quantitative variables and frequencies (i.e., count and percentages) for qualitative variables if not stated otherwise. The statistical analysis of demographic, safety and efficacy data will be performed at the Biometry Unit of the CRO.

Not available data will be evaluated as detailed in § 13.5. The statistical analysis of demographic, safety and efficacy data will be performed using SAS® version 9.3 (TS1M1) or higher (the actual version will be stated in the final report).

13.1 Analysis Sets

The following analysis sets will be considered:

Safety set: All patients who received at least a fraction of the dose of the investigational product.

Intention-to-treat (ITT): all randomized patients.

Per Protocol Set (PPS): all randomized patients who received the treatment without any major deviation from the protocol.

The exclusion of patients from the analysis sets will be discussed during a blind review meeting that will be held before database lock and complete unblinding. Subjects will be evaluated according to the treatment they were assigned to for the primary efficacy analysis (ITT, PPS) and according to the treatment they actually receive for the Safety set.

Data analysis for primary efficacy outcomes will be performed using the ITT set. A sensitivity analysis using the PP Set will also be performed for the primary endpoint. Safety parameters will be analyzed on the Safety set.

13.2 Sample size and power considerations

Considering the non-inferiority nature of the study, the hypotheses testing to be assessed is:
H0: $p2-p1 \leq 0 - m$
H1: $p2-p1 > 0 - m$
where m is the non-inferiority margin.

The test treatment will be considered not to be inferior to the reference treatment if the two treatments do not differ by more than a margin m.

Given the following parameters:
• Ratio is the ratio between the number of subjects in the test treatment arm and that in the reference treatment arm;
• α is Type I error rate;
• Power is the statistical power of the test (1 - type II error rate);
• p1 is the expected success rate in the reference treatment;
• p2 is the expected success rate in the test treatment;
• m is the non-inferiority margin,

and assuming an expected success rate of 0.85 in both the test (p2) and reference treatment (p1) arms, a non-inferiority margin of m = 0.25 and a ratio=1, a sample size of 33 subjects in each treatment arm is estimated to be sufficient at a one-sided 2.5% significance level and a power of 80% to reject the null hypothesis of inferiority.

The total number of subjects to be enrolled is therefore 66.

Furthermore, assuming a drop-out rate of 10%, 74 subjects would be needed to have 66 completers.

13.3 Expected success rate and non-inferiority margin

The successful rate of 85% for the study sample size calculation was based on the results obtained in the previous 3 clinical trials with chloroprocaine 3% gel (89-92%) in adult populations (12-14), taking into consideration the fact that the present study is conducted in a pediatric population and that the primary endpoint is only defined as score 0 (no pain) on both the WBFPS scale for children or minors aged 3-17 years and the observational FLACC scale for the smaller children (0-<3 years), whereas it is expected that several children will score also mild discomfort (score 2 on WBFPS scale and score 1 on the FLACC scale – see below).

The non-inferiority margin was chosen on the basis of clinical considerations, taking into account that the proportion of success based only on score 0, which was selected for the primary endpoint evaluation according to FDA request, could be lower than expected, both for the Test and for the Reference formulation.
In fact, it has been reported by clinicians that in children a mild discomfort could be felt after eye drops administration and during anesthesia evaluation using an eye spear sponge. This mild discomfort may not be completely discernible from pain sensation, especially in younger children, no matter how efficient the ocular conjunctiva anesthesia is. This could lead the children (WBFPS) or the observer (FLACC scale) to indicate a higher score than score 0 even when conjunctival anesthesia is present.
In a study of pain ratings using vignettes, Chambers and Craig (25) suggested that the presence of smiling faces slightly biased pain ratings away from the no pain range of spectrum. A similar conclusion was reported in a study of pain ratings among children after venipuncture (26). Therefore, reaching discrete score 2 of the scale (second step after the first face on the WBFPS; see Figure 2) is something expected, not to be considered pain-related in the clinical context, and in line with the anesthetic features observed when ocular local anesthetics are topically administered.

A neonate or infant is normally “Relaxed and comfortable” (overall score 0 on the FLACC scale) when he/she is in a normal/known situation, in the absence of noxious stimuli. Even only bringing a non-familiar object (e.g., eye drop or spear sponge) close to the neonate or infant eye(s) is likely to provoke an untoward reaction. Following a prospective observational study at a urban tertiary children’s hospital in infants aged 6 to 22 months, Babl *et al.* (27) concluded that FLACC scores can be higher than expected during nonpainful procedures and during the restraint phase of painful procedures. Similarly, Crellin *et al.* (23) reported that scores for children presumed not to be in pain (baseline, preparation and non-painful procedures) corresponded to 1.6±2.5, indicating a wide variability in baseline values in the absence of pain.

Thus, from the above reported considerations, it follows that the percentage of success based on score 0 in the study pediatric population could be slightly lower than the previously reported success rates in adult studies, both for the Test and for the Reference product.

In any case, the present study is aimed at claiming the non-inferiority of chloroprocaine 3% versus oxybuprocaine chlorhydrate 0.4%, which means that the proportion of success for the Test product will be considered not to be inferior to the Reference treatment if they do not differ by more than the chosen margin (see § 13.7).

13.4 Intercurrent events

According to the EMA addendum to ICH E9(R1) about estimands and sensitivity analysis (24), the primary efficacy analysis will be conducted under a "treatment policy strategy".

Under the treatment policy strategy, if an intercurrent event has occurred or not is irrelevant, the data will be collected and analysed regardless. For example, if a patient took rescue medication, or discontinued from the trial, the data post the event would be included in the analyses. This policy reflects the intention-to-treat (ITT) principle.

Indeed, in this trial, in the case of unsuccessful anesthesia requiring the use of rescue anesthesia to proceed with the diagnostic procedure, the patients will be regarded as failure due to a score greater than 0.

If the primary efficacy parameter cannot be collected due to complications preventing to assess anesthesia success, a "composite strategy" for the handling of missing data will be used and the patient will be regarded as failure.

13.5 Handling of missing data

13.5.1 Methods for replacing missing data

- Primary efficacy parameter: patients with missing data for the primary efficacy parameter will be imputed as failure.
- Safety parameters: no imputation will be done for the safety parameters.

13.5.2 Replacement rules for each analysis set

In general, missing data will be replaced according to methods specified in § 13.5.1. In particular:

- Intention to Treat (ITT): all missing values of the primary endpoint will be treated as a failure of the anesthesia
- Per Protocol Set (PP): no replacement of missing data is required for the primary endpoint.
- Safety Set: no replacement of missing data is required for the safety endpoints.

13.6 Demographic, baseline and background characteristics

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

13.7 Analysis of efficacy parameters

Conjunctival anaesthesia scores for the right eye (study eye) and for the left eye (non-study eye) will be listed by subjects and summarized by frequency and descriptive statistics overall (i.e. for the 0-3 and 3-17 years age groups together) and by age group (corresponding to the two different scales). Scores will be dichotomized as success (score = 0) / no success (score > 1) on either scale (WBFPS or FLACC) and summarized by frequency overall (i.e. for the 0-3 and 3-17 year age groups together) and by age group (corresponding to the two different scales).

13.7.1 Primary analysis

The primary analysis (right eye only) will be performed on the ITT set. A non-inferiority test will be used to compare the proportion of success in each treatment group. The difference in proportions and its one-sided 95% confidence interval will be derived from the SAS FREQ procedure using RISKDIFF option and specifying the NONINFERIORITY (or NONINF) to request the Farrington-Manning score test for noninferiority. The significance of the test and therefore the non-inferiority of the Test treatment versus the Reference treatment will be confirmed if the lower limit of the 95% confidence interval is greater than the noninferiority margin (-0.25).

A sensitivity analysis will be done on the PP set, using the same methodology applied for the ITT set.

13.8 Safety and tolerability evaluation

13.8.1 AEs

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

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

- PTAEs: all AEs occurring before the first dose of investigational product
- TEAEs: all AEs occurring or worsening after the first dose of investigational product

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarized 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.

13.8.2 Slit lamp examination/Binocular Indirect Ophthalmoscopy

Scores or values for Slit lamp examination/Binocular Indirect Ophthalmoscopy parameters and their changes from baseline will be listed and summarized for each eye using descriptive statistics (mean, SD, CV%, minimum, median and maximum).

13.8.3 Vital signs (blood pressure and heart rate)

Vital signs values at screening and post-dose will be listed and summarized by descriptive statistics.

13.8.4 Product global tolerability

Scores of the product overall tolerance assessment will be listed and summarized by treatment and eye using descriptive statistics.

13.8.5 Slit lamp examination/Binocular Indirect Ophthalmoscopy – additional assessments

Scores or values for the additional assessments at the Slit lamp or performed by Binocular indirect ophthalmoscopy will be listed, if applicable.

14 DATA MANAGEMENT PROCEDURES

14.1 Data collection – electronic CRFs

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He must also check that the data reported in the eCRF correspond to those in the subject's source documents.
The eCRF should be filled out in English. Any correction to the eCRF entries must be carried out by the Investigator or a designated member of staff. The Investigator must provide a reasonable explanation for all missing data.

14.2 Unique patient identifier

All the study subjects who sign the informed assent form and/or with the informed consent form signed by parents/legal representative(s)for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model.
The unique subject identifier consists of the Sponsor study code (i.e., CHL.3-01-2021-M), the 2-digit site number (i.e., 01), the 6-digit screening number (e.g., 01-001, 01-002…., etc.) and, if applicable, the 3-digit subject randomization number (e.g., 101, 102, etc.). Study code, site number, screening number and subject randomization number are separated by slashes ("/"). The last 10 digits of the unique subject identifier (randomized subjects), corresponding to the subject screening and subject randomization numbers separated by a slash, or the last 6 digits of the unique subject identifier (not randomized subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report (CSR).

14.3 Data management

Database and eCRF design will be set-up by the CRO Biometry Unit before the start of the study. Verification and cross-verification of the data entered by the study personnel will be automatically performed by the system, according to predefined nature/type of the data, value ranges and rules. All rules applied by the system to check specific items will be detailed in the Data Validation Plan (DVP). Queries will be automatically generated by the system for all data found to be inconsistent, incorrect or missing. All changes performed by the Investigators/authorized users will be tracked by the system's audit trail.
Once all data are entered in the eCRF and all outstanding queries are solved and the Monitor complete the Source Data Verification (SDV), the Data Manager will verify the correctness of the answers and the Investigators will approve (sign) the data of the subjects' eCRF.
Data management standards and procedures will be stated in the Data Management Plan (DMP) in agreement with the Sponsor.

14.3.1 Coding dictionaries

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

15 STUDY MONITORING AND AUDITING

15.1 Monitoring

The monitoring visits will be conducted by the appointed CRO/CRAs and the Sponsor.

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

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

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

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.

15.2 Quality Control and Quality Assurance

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

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

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

The Sponsor may transfer any or all 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.

15.3 Applicable SOPs

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

15.4 Data access

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

15.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

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

16 DEFINITION AND HANDLING OF AEs AND SAEs

16.1 Applicable SOPs

AEs will be recorded throughout the study.

AEs definition, classification and management will follow the Sponsor SOP, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the study sites. A summary of AE definition, classification and management is reported below.

16.2 Definitions

- **Adverse event (AE)**

Any untoward medical occurrence in a patient or clinical investigation patient 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. The following medical occurrences and clinical investigations are the only clinically significant events which, according to the investigator judgement, can be defined and recorded as PTAEs:

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

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

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

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient 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 patient'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, § 7 of 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.

16.3 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent/assent
- 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 patients) must be recorded only if it is an ADR, according to the investigator's judgment.

16.4 AEs recording

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

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
3. Start Date/Time: start date/time of the adverse event or
4. Follow-up Date/Time: follow-up date/time of the adverse event
5. End Date/Time: end date/time of the adverse event
6. Affected Body Area: anatomical location relevant for the event; in case of an ophthalmological AE, left or right eye must be recorded

7. Whether the adverse event starts before or after the first intake of the study drug or whether the adverse event has worsened or not after the first intake of the study drug
8. Last Study Drug Administration Date/Time Before Onset: if the adverse event started after the first administration of the study drug, the date/time of last administration of the study drug before the onset of the adverse event or Last Study Drug Administration Date/Time Before Worsening: In case of treatment emergent adverse event, the date/time of the last administration of the study drug(s) before the worsening of the adverse event.
9. Investigator's opinion about the reasonable possibility of a causal relationship with the study drug.
10. Investigator's opinion about other causal relationship (e.g. non study drug, concomitant therapy, study device, etc.).
11. Severity: the severity or intensity of the event
    1 Mild
    2 Moderate
    3 Severe
12. Pattern: Used to indicate the pattern of the event over time
    1 Single Event
    2 Continuous
    3 Intermittent
13. Serious Adverse Event
14. Action Taken with Study Drug: describes changes to the study drug as a result of the event. It is specifically for actions taken with the study drug
    1 Dose Not Changed
    2 Dose Increased
    3 Dose Reduced
    4 Drug Interrupted (i.e. temporary stop)
    5 Drug Withdrawn (i.e. definitive stop)
    6 Not Applicable (e.g. drug administration not started yet or completed)
    7 Unknown
15. Concomitant Therapy: if a concomitant therapy is given, it must be reported in the specific eCRF forms
16. Study Discontinuation: if the adverse event causes the patient to be discontinued from the study
17. Other Action Taken: other actions taken as a result of the event that are unrelated to dose adjustments of study drug
18. Outcome: Outcome of the event
    1 Recovered/Resolved
    2 Recovered/Resolved with Sequelae
    3 Recovering/Resolving
    4 Not Recovered/Not Resolved
    5 Fatal
    6 Unknown

16.5 SAEs reporting

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. 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.

16.6 SUSARs management

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

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

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.
The minimum information to be reported includes:

- Valid EU trial number
- Sponsor study number
- One identifiable coded patient
- 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).

16.7 Other events qualified for expedited reporting

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

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g.: a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported to the investigator by the patient.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the patients, 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 patient 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.

16.8 Reporting of SUSARs to the Eudravigilance database

Reporting of suspected unexpected serious adverse reactions to the Eudravigilance database is performed by the Sponsor according to the regulatory requirements.

16.9 SAEs: contacts

Sponsor Pharmacovigilance (PV) can be contacted using the phone and fax numbers stated in this protocol. SAEs must be reported on SAE forms in the eCRF where Sponsor PV can access them directly. In case of unexpected technical problems with the eCRF, 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

17 ETHICAL CONSIDERATIONS

17.1 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 relevant Ethics 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 current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable international and local law requirements.

17.2 Informed Consent and Child Assent Form

Before being enrolled in the clinical study, the subjects (children/parent(s)/legal representative(s)) must have expressed their consent/assent (if applicable) 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. If requested, older adolescents may have a private conversation (without parents) with the trial personnel about confidential/sensitive issues.

The informed consent must be signed by both parents/legal representative(s), according to the ICH-GCP recommendations, unless only one has legal authority. A suitable informed assent will be submitted to the pediatric patients for the signature/approval, if applicable, on the basis of their age:

- In children <6 years of age, not capable of understanding the information related to the study, it is not possible to obtain assent, and the understanding of research is not expected. Where the child has some capacity for understanding (pre-school children), age-appropriate information will be given even though it will not be possible to obtain assent. According to their age and maturity they will be given the opportunity to form an opinion or decision and their agreement should be requested systematically. Their refusal or dissent should be respected, objections should be analysed. Resistance of very young children should be identified and discussed with legal representatives.
- In children from 6 up to 11 included the assent will be obtained, whenever possible, in writing.
- Adolescents aged from 12 up 17 years will provide oral and written informed consent to participate in the clinical trial in addition to the requirement for the consent of parents or the legal representatives.

The information sheets and informed consent/assent forms will be prepared in the local language and submitted to the regulatory authorities for approval. The documents will include all the elements required by law according to the ICH-GCP recommendations.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

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

Adequate time and opportunity to satisfy questions will be given to the subjects (children/parent(s)/legal representative(s)).

During the consent/assent discussion it will be verified that everyone (including the child) has understood the information.

Dissent is the explicit wish of a minor who is capable of forming an opinion to refuse participation in, or to withdraw from, the clinical trial at any time. The lack of assent, written or oral as foreseen, is equivalent to the minor's refusal to participate, i.e. dissent. A lack of agreement by the child may or may not be equivalent to dissent, depending on the maturity of the minor to express agreement. The minor capable of forming an opinion may express dissent verbally, but also in other ways. Dissent will be respected by the investigator and properly recorded. Objections should be analysed (reason), and possible help sought for anticipated burden (fear, distress etc.).

Subjects and their parents/legal representative(s) will be provided with additional information in local language regarding the information to on the processing of their personal data according to the European General Data Protection Regulation (GDPR, EU Regulation n 2016/679).

Informed assent, when applicable, will be obtained in writing from the patient.

For what concerns parents/legal representative(s) informed consent, unless only one has legal authority, the following situations are possible in order of preference:

1	Both parents/legal representative(s) are present at the site	Both parents/legal representative(s) will sign the paper informed consent
2	Only one of the parents/legal representative(s) can be present at the site	The Investigator or a deputy will anticipate the study information remotely (e.g., electronically, in paper through the partner etc.) to the other parent/legal representative. After suitable time to review the documents, he/she will be contacted by the Investigator (or a deputy) by phone or other remote systems and will have the possibility and ample time to discuss the study with the concerned clinical staff

		member(s)/Investigator and ask questions. The Investigator (or deputy) will make any reasonable effort to confirm the identity of the parent/legal representative. Thereafter the informed consent will be expressed through an electronic Informed Consent platform with strong electronic signature features.
3	Only one of the parents/legal representative(s) can be present at the site and the other one is not comfortable or unwilling to use electronic methods	The Investigator or a deputy will anticipate the study information remotely (e.g., electronically, in paper through the partner etc.) to the other parent/legal representative. After suitable time to review the documents, he/she will be contacted by the Investigator (or a deputy) by phone or other remote systems and will have the possibility and ample time to discuss the study and ask questions. The parent/legal representative who cannot attend the clinical site will sign a paper copy of the informed consent and provide it to the site through the partner together with a delegation letter and a signed copy of a personal ID document.

Whatever procedure is followed, the complete assent/informed consent process will be documented and completed before any procedure specific to the clinical study is performed.

To ensure medical confidentiality and data protection, the signed informed consent/assent forms will be stored in the Investigator's study file (if in paper) or in a secure electronic system (in case of eConsent) according to the regulatory requirements. The Investigator will allow inspection of the forms by authorised representatives of the Sponsor, EC members and regulatory authorities. He/she will confirm, by signing and dating the forms (in paper or through the eConsent platform as applicable), that informed consent/assent has been obtained.

17.3 Criteria for patient's withdrawal

Participants will be free to discontinue the trial at any time without giving their reasons. A participant must be withdrawn in the event of any of the following:

- withdrawal of the subject's consent
- discovery of ineligibility
- administrative reasons

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. In case of premature withdrawal from the trial, the investigations scheduled for the last visit should be performed, if possible with focus on the most relevant assessments. In any case, the appropriate eCRF section must be completed.

17.4 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 IMP, e.g. due to:
  - Evidence of inefficacy of the IMP,
  - 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 IMP(s) from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) 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.

17.5 Insurance policy

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

17.6 Study termination

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

18 ADMINISTRATIVE PROCEDURES

18.1 Material supplied to the clinical center

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

- final version of the study protocol
- access to eCRF
- copy of the Investigator's Brochure (IB) for the Test IMP and of the SmPC or Patient Information Leaflet for the Reference IMP
- informed consent, assent forms and access to the eConsent platform

Moreover, before the start of the study, the Investigator(s) will be provided with the documents such as: 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.

18.2 Protocol amendments/modifications

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/modifications should be made by mutual agreement between the investigator and the sponsor. Any amendment/modification must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment/modification becomes then part of the protocol.

All amendments/modifications will be sent to the EC and concerned Competent Authorities, according to the current regulations in the EU.

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

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

18.3 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRF and in all required reports.

The investigator must keep source documents for each patient in the study. All information on the eCRF must be traceable to these source documents, which are generally stored in the patient's medical file. The source documents should contain all demographic and medical information, including ECGs etc., and the original signed informed consent/assent forms.

Data reported in the eCRF, 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 patients including ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent/assent forms (including eConsents), confidential patients identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final clinical 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.

18.4 Study patients' recruitment

Study participants will be recruited at each clinical center among the patients attending the clinic.

18.5 Confidentiality and data protection

By signing this protocol, the Investigators and the CRO agree to keep all the information provided by the Sponsor in strict confidentiality and to request the same confidentiality from their staff. Study documents provided by the Sponsor (protocols, IB, eCRF and other materials) will be stored appropriately to ensure confidentiality. The information provided by the Sponsor to the Investigators 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/assent from the subjects wishing to participate in the study and their parents/legal representative(s).

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

18.6 Measures implemented for data security breaches

The CRO operates in Switzerland and could manage Personal Data of subjects from Switzerland, Europe and the rest of the world.

Swiss data protection legislation is closely tied to EU regulations and transfer and processing of data in Switzerland is permitted according to art. 45 (1) of GDPR that states that transfer

may take place where the Commission has decided that the third country ensures an adequate level of protection. On 26 July 2000, the European Commission decided in Commission Decision 2000/518/EC (Official Journal L 215/1 of 25.8.2000) that the Swiss law provides adequate protection of personal data.

The CRO has implemented numerous technical and organizational measures to ensure the most complete protection of personal data.
The processing of personal data by the CRO is always in line with the GDPR and the applicable Swiss data protection regulations.
Data Protection by design and by default principles is built-in in all CRO processes.
Routine Study Risk Evaluation Meetings ensure that adequate measures are built-in in the studies since the early design. Data Protection training is foreseen for all employee to ensure that a workplace culture and awareness of Data Protection is diffused in the CRO.

Contractors and consultants are made aware of and required to comply with the CRO data protection requirements.

The CRO Management has established an independent Data Protection Officer on the basis of professional qualities and, in particular, expert knowledge of data protection law and practices and the ability to fulfil the GDPR DPO tasks.

The CRO has established a specific Register of Processing Activities according to GDPR art.30.
Where a type of data processing is likely to result in a high risk to the rights and freedoms of natural persons, the CRO carries out an assessment of the impact of the envisaged processing operations on the protection of personal data (Data Protection Impact Assessment, DPIA).

The CRO ensures that all key data subjects' rights are respected in agreement with requirements and timelines stated in applicable Data Protection Regulations.
The CRO has a public Privacy Policy that is accessible on the corporate web site (https://www.croalliance.com/privacy-policy/).

The CRO has a specific Data Retention Policy for the different types of data.
The CRO tracks, properly processes, and reports any Data Protection related incident.
The CRO adopts suitable technical security measures (limitations and controls of the access to the data, protection from any unauthorized data access and/or modifications, safeguard of the data and theft, loss and destruction prevention, periodical check of restore procedures, offsite daily backups, routine tests, firewall, antivirus, periodical penetration testings, encryption techniques etc.) to ensure the maximum confidentiality of the Personal Data and guarantee a level of security commensurate with the risks, to prevent the risks of destruction and loss, accidental or otherwise, of the Personal Data and of unauthorised access or unlawful processing.

The CRO adopts suitable organizational measures (checks on accesses to premises and offices, adequate systems for authentication and authorization of the staff authorized, good data protection practices, tidy desk practice, secure document shredding, secure storage etc.) to ensure the maximum confidentiality of the Personal Data and guarantee a level of security commensurate with the risks, to prevent the risks of destruction and loss, accidental or otherwise, of the Personal Data and of unauthorised access or unlawful processing.

18.7 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 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.
The study will be registered and published in clinicaltrials.gov.

18.8 Submission of summary results

Summary results will be submitted through the CTIS (Clinical Trial Information System) within 6 months from study end, according to the requirements of the Clinical Trial Regulation (EU) 536/2014.

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Appendix – Investigators signature pages

Investigator Signature Page

The signature below:

Confirms my agreement to conduct the trial in compliance with the protocol, the Declaration of Helsinki, the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), the Clinical Trial Regulation (EU) 536/2014, General Data Protection Regulation and the applicable local law requirements, including. 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 the Sponsor informs me these documents are no longer needed, according to the applicable local and international regulations,
- 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 to supervise any individual or party to whom I will delegate trial-related duties and functions at the trial site,
- 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*