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

Summary

EudraCT number	2019-001660-30
Trial protocol	SK ES IT
Global end of trial date	09 March 2021

Results information

Result version number	v1 (current)
This version publication date	19 May 2022
First version publication date	19 May 2022

Trial information

Trial identification

Sponsor protocol code	CHL.3/01-2019/M

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04685538
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sintetica SA
Sponsor organisation address	Via Penate 5, Mendrisio, Switzerland, 6850
Public contact	Clinical Operations, Iris Pharma, +33 493594959,
Scientific contact	Clinical Operations, Iris Pharma, +33 493594959,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Equivalence evaluation of Test versus Reference products in terms of proportion of subjects with a successful surface anesthesia for cataract surgery, without any supplementation at T4 (just before Intra Ocular Lens implantation)

Successful surface anesthesia & Supplementation are defined in the study protocol.

Protection of trial subjects:

For ensuring the protection of the subjects, inclusion and exclusion criteria were assessed at visit 1 for and the proper safety assessemtn and adverse evente collection thoughout the whole study duration.

Background therapy:

not applicable

Evidence for comparator:

Current practices for ocular topical anesthesia in Europe include topical liquid Oxybuprocaine, Tetracaine and Lidocaine. Tetracaine was chosen among them.

Actual start date of recruitment	27 April 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 130
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Italy: 263
Worldwide total number of subjects	410
EEA total number of subjects	410

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	112
From 65 to 84 years	282
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Patients scheduled to undergo cataract surgery in a single eye at a time fo a day surgery

Pre-assignment

Screening details:

Visit 1: between Day -90 and Day -1
ICF;Verification of incl/excl criteria, demography data;pregnancy test;Ocular and systemic medical and surgical histories;Previous and ConMeds;Ocular symptoms;Best-far corrected visual acuity;Slit lamp examination;IOP;Endothelial cell count;Fundoscopy;Pachymetry;Macular optical coherence tomography;CV parameters

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a masked-observer study.
The surgeon placing the gel/drop was aware of the treatment administered. He/she was not to be further involved in patient's care, and data recording and all the study variables were to be evaluated and recorded by another investigator
The surgeon was to be only involved in patient surgery and in satisfaction assessment.
An independent masked investigator was to evaluate sensory block and safety parameters for each patient.
The patient was to be masked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Chloroprocaine

Arm description:

Chloroprocaine 3% Gel ophthalmic gel

Arm type	Experimental
Investigational medicinal product name	Chloroprocaine hydrochloride 3% eye gel
Investigational medicinal product code	CAS number: 3858-89-7
Other name	
Pharmaceutical forms	Eye gel
Routes of administration	Conjunctival use

Dosage and administration details:

Dose: 1 drop
Frequency: 3 times
Administration route: Topical instillation

Arm title	Tetracaine

Arm description:

Tetracaine 0.5% eye-drop ophthalmic solution

Arm type	Active comparator
Investigational medicinal product name	Tetracaine 0.5% eye-drop ophthalmic solution
Investigational medicinal product code	NDC 69292-0317-15
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

Dose: 1 drop
Frequency: 3 times
Administration route: Topical instillation

Number of subjects in period 1	Chloroprocaine	Tetracaine
Started	205	205
Completed	163	169
Not completed	42	36
Adverse event, non-fatal	-	1
not randomized	-	32
discontinuated before treatment	32	-
discontinued before treatment	-	1
Lost to follow-up	-	2
Protocol deviation	10	-

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
Number of patients enrolled and randomized to receive either IMP or active comparator	

Reporting group values	overall trial	Total	
Number of subjects	410	410	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	112	112	
From 65-84 years	282	282	
85 years and over	16	16	
Age continuous Units: years			
arithmetic mean	69.37		
standard deviation	± 10.11	-	
Gender categorical Units: Subjects			
Female	228	228	
Male	182	182	

Subject analysis sets	
Subject analysis set title	Enrolled set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients enrolled in the study.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients enrolled in the study for whom any follow-up efficacy information was available.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients enrolled in the study, for whom there was evidence that they used study medication and for whom any follow-up information was available	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description:	
ll patients of the FAS who did not show any major protocol violation.	

Reporting group values	Enrolled set	FAS	Safety set
Number of subjects	410	338	338
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	112	85	85
From 65-84 years	282	239	239
85 years and over	16	13	13
Age continuous Units: years			
arithmetic mean	69.37	69.58	69.58
standard deviation	± 10.11	± 10.12	± 10.12
Gender categorical Units: Subjects			
Female	228	180	180
Male	182	158	158

Reporting group values	PP set		
Number of subjects	332		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	85		
From 65-84 years	237		
85 years and over	12		
Age continuous Units: years			
arithmetic mean	69.56		
standard deviation	± 10.12		
Gender categorical Units: Subjects			
Female	176		
Male	156		

End points

End points reporting groups

Reporting group title	Chloroprocaine
Reporting group description: Chloroprocaine 3% Gel ophthalmic gel	
Reporting group title	Tetracaine
Reporting group description: Tetracaine 0.5% eye-drop ophthalmic solution	
Subject analysis set title	Enrolled set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients enrolled in the study.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: All patients enrolled in the study for whom any follow-up efficacy information was available.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients enrolled in the study, for whom there was evidence that they used study medication and for whom any follow-up information was available	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description: ll patients of the FAS who did not show any major protocol violation.	

Primary: Successful surface anesthesia_Chloroprocaine vs Tetracaine

End point title	Successful surface anesthesia_Chloroprocaine vs Tetracaine
End point description: Equivalence evaluation of Chloroprocaine 3% Gel versus Tetracaine 0.5% eye-drop products in terms of proportion of patients with a successful surface anesthesia for cataract surgery, without any supplementation at T4 (just before Intra Ocular Lens implantation).	
End point type	Primary
End point timeframe: at T4 in Visit 2	

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[1]	169[2]		
Units: number of subjects				
Anesthesia Success_PP_Yes	150	153		
Anesthesia Success_PP_No	13	16		
Anesthesia Success_FAS_Yes	152	153		
Anesthesia Success_FAS_No	14	19		

Notes:

[1] - 163 for the PP
166 for the FAS
[2] - 169 for the PP
172 for the FAS

Attachments (see zip file)	surface anesthesia at T4_V2.png

Statistical analyses

Statistical analysis title	Proportion of successful surface anesthesia at T4
Comparison groups	Tetracaine v Chloroprocaine
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	estimated difference in proportions
Point estimate	1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10
upper limit	10
Variability estimate	Standard deviation

Secondary: Successful surface anesthesia at T1, T2, T3 during Visit 2_PP

End point title	Successful surface anesthesia at T1, T2, T3 during Visit 2_PP
End point description:	
Time points: T1 - Just before first incision T2 - End of capsulorhexis T3 - End of phacoemulsification	
End point type	Secondary
End point timeframe:	
during Visit 2	

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	169		
Units: number of subjects				
Successful surface anesthesia_T1_Yes	155	163		
Successful surface anesthesia_T1_No	8	6		
Successful surface anesthesia_T2_Yes	159	163		
Successful surface anesthesia_T2_No	4	6		
Successful surface anesthesia_T3_Yes	152	151		
Successful surface anesthesia_T3_No	11	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular symptoms analysis - Safety set

End point title	Ocular symptoms analysis - Safety set

End point description:

Ocular symptoms (pain, irritation/burning/stinging, photophobia, foreign body sensation) will be graded by the patients according to the following scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

End point type	Secondary

End point timeframe:

during the study (Visit 1-Selection and Visit 4-Final)

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	172[3]		
Units: grading				
arithmetic mean (standard deviation)				
Foreign body sensation_V1_study eye	0.08 (± 0.32)	0.06 (± 0.33)		
Foreign body sensation_V4_study eye	0.19 (± 0.43)	0.17 (± 0.41)		
Irritation/burning/stinging_V1_study eye	0.11 (± 0.33)	0.11 (± 0.37)		
Irritation/burning/stinging_V4_study eye	0.11 (± 0.36)	0.15 (± 0.39)		
Pain_V1_study eye	0.01 (± 0.11)	0.01 (± 0.08)		
Pain_V4_study eye	0.05 (± 0.24)	0.05 (± 0.24)		
Photophobia_V1_study eye	0.13 (± 0.42)	0.08 (± 0.35)		
Photophobia_V4_study eye	0.18 (± 0.50)	0.11 (± 0.36)		

Notes:

[3] - 169 for all the assessment at visit 4

Statistical analyses

No statistical analyses for this end point

Secondary: Time to obtain sufficient anesthesia and total time (duration) of anesthesia_PP

End point title	Time to obtain sufficient anesthesia and total time (duration) of anesthesia_PP

End point description:

Note: For patients who achieved anesthesia in a time frame of less than a minute, time to obtain anesthesia is set at 1 min.

End point type	Secondary

End point timeframe:
at visit 2

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	169		
Units: minute				
arithmetic mean (standard deviation)				
Time To Obtain Sufficient Anesthesia	1.35 (± 0.87)	1.57 (± 1.85)		
Total Duration Of Anesthesia	21.57 (± 12.26)	22.04 (± 12.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intraocular pressure analysis - Safety set

End point title	Intraocular pressure analysis - Safety set

End point description:

End point type	Secondary

End point timeframe:
at V1 and V4

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	172		
Units: mmHg				
arithmetic mean (standard deviation)				
IOP_V1_study eye	15.10 (± 2.70)	15.02 (± 2.46)		
IOP_V4_study eye	14.73 (± 2.78)	14.85 (± 3.06)		
IOP_V1_other eye	14.90 (± 2.41)	14.88 (± 2.47)		
IOP_V4_other eye	14.80 (± 2.50)	14.95 (± 2.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy analysis - Safety set

End point title	Fundoscopy analysis - Safety set

End point description:

End point type	Secondary

End point timeframe:
at V1 and at V4

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	172		
Units: number of subjects				
Macula_V1_study eye_abnormal	15	16		
Macula_V1_study eye_normal	149	152		
Macula_V4_study eye_abnormal	13	10		
Macula_V4_study eye_normal	152	159		
Optic nerve_V1_study eye_abnormal	16	16		
Optic nerve_V1_study eye_normal	149	153		
Optic nerve_V4_study eye_abnormalv	12	10		
Optic nerve_V4_study eye_normal	153	159		
Retina_V1_study eye_abnormal	13	11		
Retina_V1_study eye_normal	152	158		
Retina_V4_study eye_abnormal	13	12		
Retina_V4_study eye_normal	152	157		
Macula_V1_other eye_abnormal	14	20		
Macula_V1_other eye_norma	151	152		
Macula_V4_other eye_abnorma	10	13		
Macula_V4_other eye_norma	156	155		
Optic nerve_V1_other eye_abnormal	17	16		
Optic nerve_V1_other eye_normal	149	156		
Optic nerve_V4_other eye_abnormal	14	10		
Optic nerve_V4_other eye_normal	152	158		
Retina_V1_other eye_abnormal	12	12		
Retina_V1_other eye_normal	156	160		
Retina_V4_other eye_abnormal	14	9		
Retina_V4_other eye_normal	152	159		

Statistical analyses

No statistical analyses for this end point

Secondary: Specular microscopy analysis - Safety set

End point title	Specular microscopy analysis - Safety set

End point description:
Endothelial Cells Count [cell/mm2]

End point type	Secondary

End point timeframe:
at V1 and at V4

End point values	Chloroprocaine	Tetracaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[4]	172[5]		
Units: cells/square millimiter				
arithmetic mean (standard deviation)				
Endothelial Cells Count_V1_study eye	2440.76 (± 378.01)	2511.89 (± 325.32)		
Endothelial Cells Count_V4_study eye	2049.88 (± 620.43)	2166.96 (± 517.41)		

Notes:

[4] - at V4, 161 subjects

[5] - at V4, 165 subjects

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from visit 2 to visit 5	
Adverse event reporting additional description: All AEs derived by spontaneous, unsolicited reports of the patients, by observation and by routine open questioning were to be collected and reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Choloroprocaine 3% gel
Reporting group description: safety set	
Reporting group title	Tetracaine 0.5% eye drop
Reporting group description: safety set	

Serious adverse events	Choloroprocaine 3% gel	Tetracaine 0.5% eye drop	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 166 (0.00%)	0 / 172 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Choloroprocaine 3% gel	Tetracaine 0.5% eye drop	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 166 (8.43%)	19 / 172 (11.05%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 166 (0.00%)	3 / 172 (1.74%)	
occurrences (all)	0	3	
intraoc			
subjects affected / exposed	1 / 166 (0.60%)	3 / 172 (1.74%)	
occurrences (all)	1	6	
Injury, poisoning and procedural			

complications			
Incision site oedema			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Corneal dystrophy			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Nervous system disorders			
Trigeminal neuralgia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Sensation of foreign body			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Corneal degeneration			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Corneal disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Corneal oedema			

subjects affected / exposed	5 / 166 (3.01%)	2 / 172 (1.16%)	
occurrences (all)	5	2	
Eye discharge			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Hyperaesthesia eye			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Iridocele			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Lens dislocation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Ocular hypertension			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 172 (0.58%)	
occurrences (all)	1	1	
Punctate keratitis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 172 (0.58%)	
occurrences (all)	1	1	
Pupillary deformity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Pupillary disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 172 (0.58%)	
occurrences (all)	0	1	
Retinal pigment epitheliopathy			
subjects affected / exposed	1 / 166 (0.60%)	0 / 172 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all)	1 / 166 (0.60%) 1	0 / 172 (0.00%) 0	
Product issues Device dislocation subjects affected / exposed occurrences (all)	 1 / 166 (0.60%) 1	 1 / 172 (0.58%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported