Clinical trial results:
Determination of the minimum local anesthetic dose (MLAD) of spinal chloroprocaine for inguinal herniorrhaphy in ambulatory surgery.

Summary

EudraCT number	2014-005469-58
Trial protocol	BE
Global end of trial date	24 January 2018

Results information

Result version number	v1 (current)
This version publication date	15 July 2020
First version publication date	15 July 2020

Trial information

Trial identification

Sponsor protocol code	AGO/2014/007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03805503
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	Corneel Heymanslaan 10, Ghent, Belgium, 9000
Public contact	Bimetra Clinics, Ghent University Hospital, +32 93320500, Bimetra.Clinics@uzgent.be
Scientific contact	Bimetra Clinics, Ghent University Hospital, +32 93320500, Bimetra.Clinics@uzgent.be

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	15 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary goal of this study is to determine the minimum effective dose for intrathecal chloroprocaine in inguinal herniorrhaphy in outpatients using a Combined Spinal Epidural (CSE) anesthesia.

Protection of trial subjects:

ethics review and approval, Informed Consent and monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2015
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	Belgium: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	7
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From the 16th September 2015 till the 7th September 2017, 12 patients participated in the study. First patient was considered as drop-out. Finally, 11 patients were included in the analysis. All participated patients were male.

Pre-assignment

Screening details:

- Outpatients for unilateral inguinal hernia repair
- ASA I - II - III

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Chloroprocainehydrochloride
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Chloroprocainehydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Chloroprocainehydrochloride 10mg/ml
Chloroprocainehydrochloride 30mg/ml (rescue medication) in the epidural space
A standard CSE procedure will be conducted. The dura will be punctured using a 27-gauge pencil-point spinal needle and a certain dose of chloroprocaine 1% will be given. After the spinal needle is withdrawn, an epidural catheter will be placed and the epidural needle will be withdrawn.
The first spinal dose of chloroprocaine 1% to start with is 50mg. This dose has been successfully used for spinal anesthesia in hernia repair outpatients to reach an adequate analgesia. Each time there will be added 2,5 microgram of sufentanil for prolongation of the analgesia. The testing interval is 2 mg.

Number of subjects in period 1	Chloroprocainehydrochloride
Started	11
Completed	11

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	11	11	
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)	7	7	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.5		
standard deviation	± 17.12	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	11	11	
height Units: cm			
arithmetic mean	179.8		
standard deviation	± 5.9	-	
weight Units: kg			
arithmetic mean	76.9		
standard deviation	± 10.67	-	

End points

End points reporting groups

Reporting group title	Chloroprocainehydrochloride

Reporting group description: -

Primary: Minimum Local Anesthetic Dose (MLAD) of chloroprocaine 1%

End point title	Minimum Local Anesthetic Dose (MLAD) of chloroprocaine 1%[1]

End point description:

MLAD of chloroprocaine 1% with 2,5 mcg of sufentanil required for a sensory anesthesia at or above the T6 dermatome at the beginning of surgery with no additional epidural anesthesia required during surgery.
There are four crossovers visible which means that the response in two consecutive patients was four times following an opposite direction and thus successful with the possibility to lower the dose in the next patient. The mean of these doses, belonging to these crossovers is the midpoint estimator and thus the ED50 (95% CI), calculated via the original Dixon and Mood method, was 54 mg (49-54).

End point type	Primary

End point timeframe:

overall study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical ananlyses available

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg				
arithmetic mean (confidence interval 95%)	54 (49 to 54)			

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Local Anesthetic Dose (MLAD) by logistic regression

End point title	Minimum Local Anesthetic Dose (MLAD) by logistic regression[2]

End point description:

The second way to determine the ED50 (95% CI) is the logistic regression method which assumes the ED50 value of 55 mg (42-64). The sigmoid dose-response curve illustrates the intersection between a response of 50% and the curve giving the corresponding dose of the ED50.

End point type	Primary

End point timeframe:

overall trial

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical ananlyses available

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg				
log mean (confidence interval 95%)	55 (42 to 64)			

Statistical analyses

No statistical analyses for this end point

Primary: MLAD determined by PAVA

End point title	MLAD determined by PAVA[3]

End point description:

End point type	Primary

End point timeframe:

overall trial

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical ananlyses available

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg				
arithmetic mean (confidence interval 95%)	56 (52 to 58)			

Statistical analyses

No statistical analyses for this end point

Secondary: time for regression of two segments

End point title	time for regression of two segments

End point description:

Time to two-segment regression varied between 15 en 55 minutes with mean value of 23 min.

End point type	Secondary

End point timeframe:

overall study

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: minutes				
arithmetic mean (standard deviation)	23 (± 13.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: ambulation

End point title	ambulation

End point description:

Motor recovery lasted from 90 to 177 minutes, depending on whether only spinal or spinal along with epidural analgesia was administered. Ambulation time fluctuated between 160 and 290 minutes

End point type	Secondary

End point timeframe:

overall study

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: minutes				
arithmetic mean (standard deviation)	251.6 (± 71.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to micturition

End point title	Time to micturition

End point description:

The time of first voiding ranged from 164 to 390 minutes and none of the patients had urinary retention which needed a bladder catheterization.

End point type	Secondary

End point timeframe:

Overall trial

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: minutes				
arithmetic mean (standard deviation)	275.5 (± 70.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: time of surgery

End point title	time of surgery

End point description:

End point type	Secondary

End point timeframe:

overall study

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: minutes				
arithmetic mean (standard deviation)	42.4 (± 11.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: motor recovery

End point title	motor recovery

End point description:

End point type	Secondary

End point timeframe:

overall trial

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: minutes				
arithmetic mean (standard deviation)	126 (± 34.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak block height

End point title	Peak block height
End point description: T1-T10	
End point type	Secondary
End point timeframe: overall trial	

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg chloroprocaine 1%				
highest sensible block reached T1 lowest dermatome at T10	54 56			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient satisfaction

End point title	Patient satisfaction
End point description:	
End point type	Secondary
End point timeframe: overall trial	

End point values	Chloroprocaine hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
satisfied	2			
highly satisfied	9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	5
Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Serious adverse events	overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)		
Cardiac disorders			
Bradycardia	Additional description: Bradycardia (< 50 bpm) has been observed in 7 patients. One patient had a HR below 40 bpm and needed intravenous administration of the drug (i.e. Atropine 0.5 mg). This particular patient had a high sensory block reaching the level of T1 dermatome.		
subjects affected / exposed	7 / 11 (63.64%)		
occurrences (all)	7		
Hypotension	Additional description: The systolic blood pressure in 7 patients and in 3 patients decreased by 20% and 30% respectively the low blood pressure. Similarly, this patient has had the highest sensory block reaching the level of T1 dermatome.		
subjects affected / exposed	7 / 11 (63.64%)		
occurrences (all)	7		

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? Yes

Date	Interruption	Restart date
24 January 2018	It was decided to end the trial because the inclusion was difficult. After 3 years, only 12 patients (including 1 drop-out) were included. The number of patents choosing for a spinal anaesthesia and gives consent to participate into a trial appears to be very small.	-

Notes:

Limitations and caveats

None reported