Clinical trial results:
Comparison of epidural Chloroprocaine 3% and Ropivacaine 0.75% for unplanned Caesarean section in labouring women who have an epidural catheter in situ

Summary

EudraCT number	2016-000298-20
Trial protocol	BE DE AT
Global end of trial date	04 June 2021

Results information

Result version number	v1 (current)
This version publication date	04 August 2022
First version publication date	04 August 2022

Trial information

Trial identification

Sponsor protocol code	CHL.3/01-2016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02919072
WHO universal trial number (UTN)	-
Other trial identifiers	study protocol: CRO-16-128

Notes:

Sponsors

Sponsor organisation name	Sintetica SA
Sponsor organisation address	Via Penate 5, Mendrisio, Switzerland, 6850
Public contact	Study Management, CROSS Research S.A., 0041 (0)91630 05 10, projectmanagement@croalliance.com
Scientific contact	Study Management, CROSS Research S.A., 0041 (0)91630 05 10, projectmanagement@croalliance.com

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	25 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to test the superiority in terms of the onset time of anaesthesia and to evaluate the quality of epidural anaesthesia and the safety of Chloroprocaine HCl 3% compared with Ropivacaine HCl 0.75% in patients with an epidural catheter in situ undergoing unplanned Caesarean section.

Protection of trial subjects:

The participating women will be presenting the study protocol, procedures and informed consent form will be signed.
Inclusion and exclusion criteria will be evaluated for grating the inclusion of selected women only.
Safety will constantly monitor throughout the whole study duration.

Background therapy:

no background therapy foreseen

Evidence for comparator:

Various local anaesthetic solutions are available and were compared in several studies looking at speed of onset of anaesthesia and quality of anaesthesia. A recent meta-analysis of available trials identified two potential epidural top-up solutions as being the most optimal: plain ropivacaine 0.75% or lidocaine 2% with epinephrine and bicarbonate. The latter solution works slightly faster but with more breakthrough pain, whilst ropivacaine provided good surgical conditions but with a small delay when compared to the lidocaine solution. The disadvantage of the lidocaine solution is that preparation time is required to mix bicarbonate, resulting in potential time-delay between decision to deliver and actual onset of anaesthesia. Therefore, the standard of practice in the UZ Leuven (study site N. 001), is 20 mL epidural ropivacaine 0.75%. In the meta-analysis by Hillyard et al. (1), chloroprocaine 3% was not evaluated because not yet available in Europe for the proposed indication.

Actual start date of recruitment	19 December 2016
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Labouring women with an epidural catheter in situ and established analgesia, in need of an unplanned Caesarean section

Pre-assignment

Screening details:

Procedures at screenign, at Visit 1 (days -1/1): ICF,Demography and lifestyle,Medical/surgical history,Physical examination,Obstetric assessment,Previous and ConMeds,Height,weight, BMI,Maternal vital signs, SpO2,Inclusion/exclusion criteria,Enrolment and Randomisation,Patient’s adverse events monitoring

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:

The study was double-blind, i.e. the Investigator and the patients were not aware of the investigational product administered. Neither the members of the clinical staff nor the CPL or the CRA, monitoring the study evaluations and procedures, had access to the randomisation code. Only the person preparing the syringe (and not involved in any other study-related procedure) and the CRA/monitor who performed the drug accountability were aware of the administered investigational product.

Arms

Are arms mutually exclusive?	Yes
Arm title	TEST (T)

Arm description:

Chloroprocaine HCl 3% (30 mg/mL), 20 mL vial

Arm type	Experimental
Investigational medicinal product name	Chloroprocaine HCl 3% (30 mg/mL)
Investigational medicinal product code	CAS number: 3858-89-7
Other name	Ampres 30 mg/mL injectable solution
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Epidural use

Dosage and administration details:

20 mL (600 mg)
The investigational epidural anaesthetic had to be administered within 10 minutes of the end of the previously established analgesia. If this time was > 10 min, the patient was to be excluded. Prior to epidural injection, the patient was transferred to the operating theatre and standard monitoring (electrocardiography, SpO2 and non-invasive blood pressure and pulse rate) was applied according to the standard hospitals' procedures. An aspiration test of the epidural catheter was performed. No prophylactic i.v. fluid bolus and no prophylactic vasopressor were administered.
In case of pain or discomfort, a 6 mL epidural top-up of the same anaesthetic, Chloroprocaine in T-group and Ropivacaine in R-group, were to be administered. The residual amount from the 20 mL vials/ampoules used for the top-up was collected from each vial/ampoule using another graduated syringe, completely sealable, and retained for drug accountability together with the empty vial/ampoule

Arm title	REFERENCE (R)

Arm description:

Naropin® 0.75% (7.5 mg/mL), 20 mL ampoule

Arm type	Active comparator

Investigational medicinal product name	Ropivacaine HCl
Investigational medicinal product code	CAS number: 132112-35-7
Other name	Naropin® 0.75% (7.5 mg/mL), 20 mL ampoule
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

20 mL (150 mg).
The investigational epidural anaesthetic had to be administered within 10 minutes of the end of the previously established analgesia. If this time was > 10 min, the patient was to be excluded. Prior to epidural injection, the patient was transferred to the operating theatre and standard monitoring (electrocardiography, SpO2 and non-invasive blood pressure and pulse rate) was applied according to the standard hospitals' procedures. An aspiration test of the epidural catheter was performed. No prophylactic i.v. fluid bolus and no prophylactic vasopressor were administered.
In case of pain or discomfort, a 6 mL epidural top-up of the same anaesthetic, Chloroprocaine in T-group and Ropivacaine in R-group, were to be administered. The residual amount from the 20 mL vials/ampoules used for the top-up was collected from each vial/ampoule using another graduated syringe, completely sealable, and retained for drug accountability together with the empty vial/ampoule

Number of subjects in period 1	TEST (T)	REFERENCE (R)
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	TEST (T)
Reporting group description:	
Chloroprocaine HCl 3% (30 mg/mL), 20 mL vial	
Reporting group title	REFERENCE (R)
Reporting group description:	
Naropin® 0.75% (7.5 mg/mL), 20 mL ampoule	

Reporting group values	TEST (T)	REFERENCE (R)	Total
Number of subjects	8	8	16
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)	8	8	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	28.8	33.3	
standard deviation	± 5.6	± 7.5	-
Gender categorical Units: Subjects			
Female	8	8	16
Male	0	0	0

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
all randomised patients who fulfilled the study protocol requirements in terms of study anaesthetic administration, i.e. patients who were administered the whole scheduled volume (at least 20 mL) and were not discontinued due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes. Missing values of time to onset of anaesthesia were to be replaced with the highest time to onset of anaesthesia detected in the corresponding treatment group. This analysis set was used for the primary efficacy analysis.	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description:	
all randomised patients who 1) fulfilled the study protocol requirements in terms of study anaesthetic administration, i.e. patients who were administered the whole scheduled volume (at least 20 mL, administered as 5 + 5 + 10 mL or 5 + 15 mL), for whom time between the end of the previously established analgesia and the start of the anaesthetic epidural injection was ≤ 10 minutes and 2)	

fulfilled the study protocol requirements in terms of primary efficacy evaluation (time to onset of anaesthesia), with no major deviations that could affect the primary efficacy results. This analysis set was used for sensitivity analysis.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

all patients who received at least one dose of the investigational medicinal product. This analysis set was used for the safety analyses

Reporting group values	FAS	PP set	Safety set
Number of subjects	13	11	16
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)	13	11	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female	13	11	16
Male	0	0	0

End points

End points reporting groups

Reporting group title	TEST (T)
Reporting group description: Chloroprocaine HCl 3% (30 mg/mL), 20 mL vial	
Reporting group title	REFERENCE (R)
Reporting group description: Naropin® 0.75% (7.5 mg/mL), 20 mL ampoule	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: all randomised patients who fulfilled the study protocol requirements in terms of study anaesthetic administration, i.e. patients who were administered the whole scheduled volume (at least 20 mL) and were not discontinued due to time between the end of the previously established analgesia and the start of the anaesthetic epidural injection > 10 minutes. Missing values of time to onset of anaesthesia were to be replaced with the highest time to onset of anaesthesia detected in the corresponding treatment group. This analysis set was used for the primary efficacy analysis.	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description: all randomised patients who 1) fulfilled the study protocol requirements in terms of study anaesthetic administration, i.e. patients who were administered the whole scheduled volume (at least 20 mL, administered as 5 + 5 + 10 mL or 5 + 15 mL), for whom time between the end of the previously established analgesia and the start of the anaesthetic epidural injection was ≤ 10 minutes and 2) fulfilled the study protocol requirements in terms of primary efficacy evaluation (time to onset of anaesthesia), with no major deviations that could affect the primary efficacy results. This analysis set was used for sensitivity analysis.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: all patients who received at least one dose of the investigational medicinal product. This analysis set was used for the safety analyses	

Primary: Time to onset of anaesthesia_FAS

End point title	Time to onset of anaesthesia_FAS
End point description: Time to onset of anaesthesia (i.e. time to reach adequate surgical conditions), defined as time from T0 to complete loss of cold sensation to the metameric level T4 (block to T4), bilateral. The median time to onset of anaesthesia was 7 min with Chloroprocaine HCl 3% and 8 min with Ropivacaine HCl 0.75%. Minimum and maximum times were, however, very similar for the two treatment groups, corresponding to 4 – 18 min for the Test and 4 – 16 min for the Reference. Also, mean values were 9.0±5.8 min for T-group and 9.1±4.0 min for R-group. Inter-individual variation was pronounced for both treatments and differences between treatment groups were not statistically significant (p-value=0.7723).	
End point type	Primary
End point timeframe: at visit 2, day 1	

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[1]	7[2]		
Units: minute				
arithmetic mean (standard deviation)	9.0 (± 5.8)	9.1 (± 4.0)		

Notes:

[1] - 6 is the number of patients analyzed in the FAS

[2] - 7 is the number of patients analyzed in the FAS

Statistical analyses

Statistical analysis title	Time to onset of anaesthesia from T0 - FAS
Comparison groups	TEST (T) v REFERENCE (R)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7723
Method	Wilcoxon Rank-Sum

Secondary: Time to onset of anaesthesia from last injection_FAS

End point title	Time to onset of anaesthesia from last injection_FAS

End point description:

The median time to onset of anesthesia was 4 min with Chloroprocaine HCl 3% and 6 min with Ropivacaine HCl 0.75%. Minimum and maximum times were, however, very similar for the two treatment groups, corresponding to 2 – 14 min for the Test and 0 – 14 min for the Reference. Also, mean values were 6.0 min for both anesthetics (6.0±5.1 min for T-group and 6±4.6 min for R-group). Inter-individual variation was pronounced for both treatments and differences between treatment groups were not statistically significant (p-value=1.000).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[3]	7[4]		
Units: minute				
arithmetic mean (standard deviation)	6.0 (± 5.1)	6.0 (± 4.6)		

Notes:

[3] - 6 is the numer of patients analyzed in the FAS

[4] - 7 is the numer of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to complete loss of touch sensation from T0_FAS

End point title	Time to complete loss of touch sensation from T0_FAS

End point description:

In the FAS, median time to complete loss of touch sensation from T0 was shorter with Chloroprocaine HCl 3% (4 min) than with Ropivacaine HCl 0.75% (13 min). Also, mean time was 9.3±9.2 and 13.3±4.1 min in T-group and R-group, respectively. However, the differences between the two treatment groups were not statistically significant (p-value=0.5151).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[5]	6[6]		
Units: minute				
arithmetic mean (standard deviation)	12.0 (± 11.3)	13.3 (± 4.1)		

Notes:

[5] - 2 is the numbert of patients analyzed in the FAS

[6] - 6 is the numbert of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum level of cold sensation loss from T0_FAS

End point title	Time to maximum level of cold sensation loss from T0_FAS

End point description:

In the FAS, median time to maximum level of loss of cold sensation from T0 was shorter with Chloroprocaine HCl 3% (7 min) than with Ropivacaine HCl 0.75% (12 min). Mean time was 10.7±7.4 and 11.4±3.2 min in T-group and R-group, respectively. Differences between the two treatment groups were not statistically significant (p-value=0.5168).
Mean time to maximum level of loss of cold sensation from T0 was similar for the Test and Reference formulations in the PP set and no statistically significant differences between treatments were present (p-value=0.9264). Median time was slightly shorter for the Test than for the Reference (8 vs 12 min).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[7]	7[8]		
Units: minute				
arithmetic mean (standard deviation)	10.7 (± 7.4)	11.4 (± 3.2)		

Notes:

[7] - 6 is the number of patients evaluated in the FAS

[8] - 7 is the number of patients evaluated in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum level of loss of pinprick sensation from T0_FAS

End point title	Time to maximum level of loss of pinprick sensation from T0_FAS

End point description:

In the FAS, time to maximum level of loss of pinprick sensation from T0 was similar for the Test and Reference formulations and no statistically significant differences between treatments were present (p-value=0.8855).
In the PP set, median time to maximum level of loss of pinprick sensation from T0 was shorter with Chloroprocaine HCl 3% (8 min) than with Ropivacaine HCl 0.75% (15 min). Mean time was 12.8±7.6 and 17.3±9.4 min in T-group and R-group, respectively. However, differences between the two treatment groups were not statistically significant (p-value=0.4621).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[9]	7[10]		
Units: minute				
arithmetic mean (standard deviation)	15.7 (± 9.8)	16.0 (± 9.3)		

Notes:

[9] - 6 is the numer of patients analyzed in the FAS

[10] - 6 is the numer of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to touch sensation complete loss from last injection_FAS

End point title	Time to touch sensation complete loss from last injection_FAS

End point description:

In the FAS, median time to complete loss of touch sensation from last injection was shorter with Chloroprocaine HCl 3% (2 min) than with Ropivacaine HCl 0.75% (10 min). Also, mean time was 6.7±8.1 and 10.0±4.6 min in T-group and R-group, respectively. However, the differences between the two treatment groups were not statistically significant (pvalue=0.4328).
Time to complete loss of touch sensation from last injection was very similar for the Test and Reference formulation in the PP set and no statistically significant differences between treatments were present (p-value=1.0000).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[11]	7[12]		
Units: minute				
arithmetic mean (standard deviation)	7.7 (± 6.7)	8.3 (± 3.5)		

Notes:

[11] - 6 is the number of patients analyzed in the FAS

[12] - 7 is the number of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum level of loss of pinprick sensation from last injection_FAS

End point title	Time to maximum level of loss of pinprick sensation from last injection_FAS

End point description:

In the FAS, time to maximum level of loss of pinprick sensation from last injection was similar for the Test and Reference formulations and no statistically significant differences between treatments were present (p-value=0.8853).
In the PP set, median time to maximum level of loss of pinprick sensation from last injection was shorter with Chloroprocaine HCl 3% (6 min) than with Ropivacaine HCl 0.75% (13 min).
Mean time was 9.6±7.0 and 14.0±9.3 min in T-group and R-group, respectively. However, differences between the two treatment groups were not statistically significant (pvalue=0.4081).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[13]	7[14]		
Units: minute				
arithmetic mean (standard deviation)	12.7 (± 9.8)	12.9 (± 9.0)		

Notes:

[13] - 6 is the numer of patients analyzed in the FAS

[14] - 7 is the numer of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum level of loss of light touch sensation from last injection_FAS

End point title	Time to maximum level of loss of light touch sensation from last injection_FAS

End point description:

In the FAS, time to maximum level of loss of light touch sensation from last injection was similar for the Test and Reference formulations and no statistically significant differences between treatments were present (p-value=1.0000).
In the PP set, median time to maximum level of loss of light touch sensation from last injection was slightly shorter with Chloroprocaine HCl 3% (6 min) than with Ropivacaine HCl 0.75% (9 min). Mean

time was 7.5±6.0 and 10.0±5.1 min in T-group and R-group, respectively. Differences between the two treatment groups were not statistically significant (pvalue= 0.4443).

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[15]	7[16]		
Units: minute				
arithmetic mean (standard deviation)	11.6 (± 10.5)	9.4 (± 4.9)		

Notes:

[15] - 5 is the number of patients analyzed in the FAS

[16] - 7 is the number of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of spinal block (0-10 cm VAS)_FAS

End point title	Quality of spinal block (0-10 cm VAS)_FAS

End point description:

Both in the FAS and in the PP set, assessment results for quality of spinal block were similar for Test and Reference, with no statistically significant differences between the two treatments (p-value for FAS=0.6282; p-value for PP set=0.4652).
Median values were 10 cm for both treatments, indicating that spinal block was deemed excellent by most subjects/anesthesiologists.

End point type	Secondary

End point timeframe:

at visit 2, day 1

End point values	TEST (T)	REFERENCE (R)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[17]	7[18]		
Units: centimetre				
arithmetic mean (standard deviation)	9.8 (± 0.4)	8.4 (± 3.7)		

Notes:

[17] - 6 is the number of patients analyzed in the FAS

[18] - 7 is the number of patients analyzed in the FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study patient:
from after informed consent signature to Follow-up visit
Neonate:
From after birth until Follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Test group_safety set
Reporting group description: -	
Reporting group title	Reference group_safety set

Reporting group description: -

Serious adverse events	Test group_safety set	Reference group_safety set	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (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	Test group_safety set	Reference group_safety set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	8 / 8 (100.00%)	
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Post procedural discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Procedural nausea			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 8 (62.50%)	7 / 8 (87.50%)	
occurrences (all)	5	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2016	ver 2.0: The amended protocol introduced the following changes: If the anesthesia had reached an adequate level with 5 or 10 mL of the investigational anaesthetic and the administration of the additional 10-15 mL could give rise to safety concerns, no additional volume would be administered, and the patient was to be excluded from the study The FAS and PP set definitions were slightly modified to exclude from the analyses patients who were withdrawn from the study because not administered the entire volume (20 mL) of study anaesthetic. The reasons for discontinuation were completed to include patients discontinued because did not receive the entire planned dose of study anaesthetic (20 mL). It was clarified that atropine 0.5 mg would be administered as an i.v. bolus A few typos were corrected.
18 October 2017	ver 3.0.The amendment introduced the following changes: Both test and reference investigational anaesthetic agents were to be administered as 5 mL plus 15 mL over 3 minutes instead of 5 mL plus 5 mL plus 10 mL over 5 minutes. Total volume was 20 mL as in the previous protocol version. This change was introduced to achieve surgical anaesthesia rapidly, taking into consideration the common clinical practice and the medical literature. With the new dose regimen, safety of the study subjects increased considering a more rapid and adequate anaesthesia for urgent Caesarean sections. The use of only one test dose as opposed to two test doses as present in the original protocol was balanced against the possible delay in establishing the blockade, which in the setting of foetal compromise may not be acceptable. No published works described the use of two test doses. The one-5 mL initial dose before the injection of the remaining dose was deemed sufficient also considering that in the study population the epidural catheter had already been tested and used to provide analgesia. In the study, before undergoing unplanned Caesarean section patients had a continuous infusion of analgesic through a previously placed epidural catheter for CSE analgesia. For a rapid onset of anaesthesia, it was fundamental that the epidural catheter was in place and used to maintain labour analgesia until anaesthetic injection. Details on the maximal allowed time between end of analgesic infusion and anaesthetic injection were added. Note to file N. 8 was issued on 08AUG2017 to clarify how to grade the correlation between VAS values for pain assessment and AE severity. Note to file Nr. 4 was issued on 07DEC2016 to clarify that, according to the clinical practice, Hetastarch/plasmalyte could be used not only at the end but also during surgery. Drug and alcohol abuse were defined according to the Investigator's opinion on the basis of the Dietary Guidelines for Americans 2015-2020

19 September 2019	ver 4.0. The amended protocol introduced the following changes: Three clinical centres were added in the study. The reason was the very low study enrolment rate due to the study inclusion/exclusion criteria, which were particularly restrictive considering the study population, i.e. women in labour undergoing unplanned Caesarean section. Because of the addition of the three new clinical centres the study design was changed from single- to multi-centre This amendment impacted the statistical methodology for the primary and secondary efficacy analyses and the study sample size. The previously planned Wilcoxon-rank sum test was in fact not applicable to the analysis of stratified data and needed to be replaced by the Van Elteren test, a widely used extension of the Wilcoxon rank-sum test for non-parametric 2-way analysis. Thus, the sample size was recalculated and the statistical methods for the primary and secondary efficacy outcome analysis modified accordingly. The CRO Clinical Project Leader and responsible Biostatistician changed. Finally, a few typos found during protocol revision were corrected and a few, minor-impact, text modifications were made.
07 August 2020	ver 6.0. The amended protocol introduced the following changes: In the previous protocol versions 4.0 and 5.0, the sample size was calculated considering a non-competitive design, i.e. each study site was to recruit an equal number of patients. The amended protocol introduced a competitive enrolment, i.e. the sites were able to enrol an unlimited number of patients until the total number of patients planned for the study had been reached. As a consequence, a new version of the randomisation list (version 5.0), containing the randomisation scheme for patients still to be enrolled at centre 001 and for all patients at centres 002, 003 and 004, was released. This amendment impacted the statistical methodology for the study sample size calculation and for the primary and secondary efficacy analyses. Thus, the sample size was recalculated and the statistical methods for the primary and secondary efficacy outcome analysis were modified accordingly (please refer to the corresponding sections in the amended protocol). Dr. Eva Roofthooft, site N. 002 Principal Investigator (PI), moved from the Department of Anesthesiology, ZNA Middelheim, Antwerpen (Belgium), to Service Anaesthesiology GZA Ziekenhuizen campus Sint-Augustinus, Wilrijk (Belgium). As a consequence site N. 2 name and address were changed in the protocol. Site N. 002 PI was Dr. Patrick Van Houwe, whereas Dr. Eva Roofthooft became the study sub-Investigator. Site N. 003 PI was Prof. Daniela Marhofer (and not Prof. Oliver Kimberger, as presented in the previous protocol version) The unique subject identifier was clarified (par. 12.2). Minor changes were introduced in the paragraph's wording. Monica Boveri replaced Angelo Vaccani for the study coordination. CTS Clinical Trial Service replaced AML Clinical Services in the blind monitoring of clinical centres N. 001 and 002 starting from AUG2020.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes: