Clinical trial results:
The ultrasound-guided multiple-injection costotransverse block for mastectomy and primary reconstructive surgery. A double blind, randomised, placebo controlled trial.

Summary

EudraCT number	2019-001016-35
Trial protocol	DK
Global end of trial date	08 December 2021

Results information

Result version number	v1 (current)
This version publication date	19 July 2023
First version publication date	19 July 2023

Trial information

Trial identification

Sponsor protocol code	ZUH-UMPR-MICB

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Sygehusvej 10, Roskilde, Denmark, 4000
Public contact	Jens Børglum, Department of Anaesthesiology and Intensive Care Medicine, Zealand University Hospital, Roskilde, +45 30700120, jens.borglum@gmail.com
Scientific contact	Jens Børglum, Department of Anaesthesiology and Intensive Care Medicine, Zealand University Hospital, Roskilde, 46323200 30700120, jens.borglum@gmail.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	01 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 December 2021
Global end of trial reached?	Yes
Global end of trial date	08 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We wish to conduct a randomized, placebo controlled and double blind study, comparing the effect of the ultrasound-guided multiple-injection costotransverse block (MICB) vs. placebo. Our aim with this study is to investigate the efficacy of the MICB vs. placebo in patients undergoing unilateral mastectomy and primary reconstructive surgery due to breast cancer. Our hypothesis is, that the unilateral MICB will significantly reduce the opioid consumption during the first 24 postoperative hours and significantly reduce the Numerical Rating Scale pain score (0-10)
and opioid related side effects.

Protection of trial subjects:

The patients were randomized and blinded to the intervention. They were closely followed-up 24 hrs postoperatively at the ward and until 14 days post surgery. The trial included a follow-up 1 year after surgery.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	34
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Female patients
breast cancer
American Society of Anesthesiologists (ASA) physical status II and III
≥18 years
Scheduled for unilateral subpectoral implant-based primary breast reconstruction

Pre-assignment period milestones

Number of subjects started	35[1]
Number of subjects completed	35

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: We aimed at 36 participating patients. During the trial period one patient in the active group was randomized but she was omitted completely from the study because she had a changed indication for surgery shortly before blockade. Thereby, she was randomized but did NOT recieve any intervention.

Period 1

Period 1 title	Trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Ropivacaine

Arm type	Active comparator
Investigational medicinal product name	Ropivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infiltration

Dosage and administration details:

50 mg at three thoracic levels (in total 150mg) within the intertransverse tissue complex.

Arm title	Placebo

Arm description:

Saline

Arm type	Placebo
Investigational medicinal product name	Saline, isotonic
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infiltration

Dosage and administration details:

10 ml isotonic Saline was injected at three thoracic levels (in total 30 ml) within the intertransverse tissue complex

Number of subjects in period 1[2]	Active	Placebo
Started	17	18
Completed	17	18

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: We aimed at 36 participating patients. During the trial period one patient in the active group was randomized but she was omitted completely from the study because she had a changed indication for surgery shortly before blockade. Thereby, she was randomized but did NOT recieve any intervention.

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Ropivacaine	
Reporting group title	Placebo
Reporting group description:	
Saline	

Reporting group values	Active	Placebo	Total
Number of subjects	17	18	35
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	50.2	52.3	
standard deviation	± 9	± 7.6	-
Gender categorical			
Units: Subjects			
Female	17	18	35
Male	0	0	0
Baseline			
Active (n = 17) Mean age (SD), years 50.2 (9) Mean weight (SD), kg 70.2 (15.5) Mean BMI (SD), kg/m2 24.6 (4.2) ASA status (1/2/3), n -/17/- Laterality (left/right), n 4/13 Mean duration of surgery (SD), min 154.8 (38.3) Mean PACU stay (SD), min 97.4 (39.7) Placebo (n = 18) Mean age (SD), years 52.3 (7.6) Mean weight (SD), kg 67.7 (8.8) Mean BMI (SD), kg/m2 24.2 (2.5) ASA status (1/2/3), n -/18/- Laterality (left/right), n 9/9 Mean duration of surgery (SD), min 171.2 (36.7) Mean PACU stay (SD), min 93.5 (32.1)			
Units: Subjects			

Baseline	17	18	35

Subject analysis sets	
Subject analysis set title	Ropivacaine
Subject analysis set type	Full analysis
Subject analysis set description: Mean age (SD), years Mean weight (SD), kg Mean BMI (SD), kg/m2 ASA status (1/2/3), n Laterality (left/right), n Mean duration of surgery (SD), min Mean PACU stay (SD), min	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Mean age (SD), years Mean weight (SD), kg Mean BMI (SD), kg/m2 ASA status (1/2/3), n Laterality (left/right), n Mean duration of surgery (SD), min Mean PACU stay (SD), min	

Reporting group values	Ropivacaine	Placebo	
Number of subjects	17	18	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 50.2 ± 9	 52.3 ± 7.6	
Gender categorical Units: Subjects			
Female Male	17 0	18 0	
Baseline			
Active (n = 17) Mean age (SD), years 50.2 (9) Mean weight (SD), kg 70.2 (15.5) Mean BMI (SD), kg/m2 24.6 (4.2) ASA status (1/2/3), n -/17/-			

Laterality (left/right), n 4/13 Mean duration of surgery (SD), min 154.8 (38.3) Mean PACU stay (SD), min 97.4 (39.7) Placebo (n = 18) Mean age (SD), years 52.3 (7.6) Mean weight (SD), kg 67.7 (8.8) Mean BMI (SD), kg/m2 24.2 (2.5) ASA status (1/2/3), n -/18/- Laterality (left/right), n 9/9 Mean duration of surgery (SD), min 171.2 (36.7) Mean PACU stay (SD), min 93.5 (32.1)			
Units: Subjects			
Baseline	17	18	

End points

End points reporting groups

Reporting group title	Active
Reporting group description: Ropivacaine	
Reporting group title	Placebo
Reporting group description: Saline	
Subject analysis set title	Ropivacaine
Subject analysis set type	Full analysis
Subject analysis set description: Mean age (SD), years Mean weight (SD), kg Mean BMI (SD), kg/m2 ASA status (1/2/3), n Laterality (left/right), n Mean duration of surgery (SD), min Mean PACU stay (SD), min	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Mean age (SD), years Mean weight (SD), kg Mean BMI (SD), kg/m2 ASA status (1/2/3), n Laterality (left/right), n Mean duration of surgery (SD), min Mean PACU stay (SD), min	

Primary: Median oral morphine equivalents

End point title	Median oral morphine equivalents
End point description:	
End point type	Primary
End point timeframe: 0-24hrs	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[1]	18[2]		
Units: mg				
median (inter-quartile range (Q1-Q3))				
PP	75 (45 to 135)	62.5 (30 to 115)		
ITT	75 (45 to 135)	62.5 (30 to 117.5)		

Notes:

[1] - PP 15
ITT 17
[2] - PP 16

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Median oral morphine equivalents

End point title	Median oral morphine equivalents

End point description:

End point type	Secondary

End point timeframe:

4
8
12
16
20hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[3]	18		
Units: mg				
median (inter-quartile range (Q1-Q3))				
4hrs	45 (30 to 80)	52.5 (0 to 85)		
8hrs	0 (0 to 15)	0 (0 to 15)		
12	0 (0 to 15)	0 (0 to 15)		
16	0 (0 to 0)	0 (0 to 0)		
20	0 (0 to 15)	0 (0 to 0)		

Notes:

[3] - PP 16
ITT 18

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Median time (IQR) to first opioid

End point title	Median time (IQR) to first opioid

End point description:

End point type	Secondary

End point timeframe:

0-24hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: minute				
median (inter-quartile range (Q1-Q3))	16 (5 to 30)	10 (4 to 31)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Median time (IQR) to first ambulation

End point title	Median time (IQR) to first ambulation

End point description:

End point type	Secondary

End point timeframe:

When admitted

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: minute				
median (inter-quartile range (Q1-Q3))	330 (240 to 480)	375 (240 to 480)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Median time (IQR) to discharge

End point title	Median time (IQR) to discharge

End point description:

End point type	Secondary

End point timeframe:

30-248

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: hours				
median (full range (min-max))	97 (70 to 117)	90.5 (68 to 120)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Opioid related side effects: nausea and vomiting

End point title	Opioid related side effects: nausea and vomiting

End point description:

End point type	Secondary

End point timeframe:

0-24hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Number	6	5		

Statistical analyses

Statistical analysis title	CHI Squared
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: QOR Mean baseline score

End point title	QOR Mean baseline score

End point description:

End point type	Secondary

End point timeframe:

0hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: number				
arithmetic mean (confidence interval 95%)	133.9 (130.1 to 137.7)	133.9 (130.1 to 137.7)		

Statistical analyses

Statistical analysis title	constrained linear mixed model
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: QOR Mean 24 hours follow-up score

End point title	QOR Mean 24 hours follow-up score

End point description:

End point type	Secondary

End point timeframe:

24hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Number				
arithmetic mean (confidence interval 95%)	105.2 (80 to 130.3)	119.59 (106.8 to 132.1)		

Statistical analyses

Statistical analysis title	constrained linear mixed model
Comparison groups	Active v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: QOR Mean 14 days follow-up score

End point title	QOR Mean 14 days follow-up score

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Number				
arithmetic mean (confidence interval 95%)	125.5 (104 to 147)	132.5 (121.5 to 143.5)		

Statistical analyses

Statistical analysis title	constrained linear mixed model
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Median max NRS scores

End point title	Median max NRS scores

End point description:

End point type	Secondary

End point timeframe:

0-24hrs

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: number				
median (inter-quartile range (Q1-Q3))				
PACU	1 (1 to 3)	3 (1 to 5)		
15	3 (2 to 4)	3 (2 to 4)		
30	3 (2 to 4)	3 (2 to 3)		
45	3 (1 to 4)	2.5 (2 to 4)		
1h	2 (1 to 3)	2 (2 to 3)		
1-4	2 (1 to 2)	1 (1 to 2)		
4-8	2 (1 to 2)	1 (1 to 2)		
8-12	1 (0 to 2)	1 (0 to 1)		
12-16	1 (0 to 2)	1 (0 to 1)		
16-20	1 (1 to 2)	1 (0 to 1)		
20-24	1 (0 to 2)	1 (0 to 1)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Median NRS scores (IQR) at block application

End point title	Median NRS scores (IQR) at block application

End point description:

End point type	Secondary

End point timeframe:
momentary

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: number				
median (inter-quartile range (Q1-Q3))				
t2	2 (1 to 5)	5.5 (4 to 7)		
t4	2 (1 to 3)	5.5 (3 to 7)		
t6	3 (1 to 3)	3 (2 to 5)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Active v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0-24hrs	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	None
Dictionary version	0
Reporting groups	
Reporting group title	Active
Reporting group description: Ropivacaine	
Reporting group title	Placebo
Reporting group description: Saline	

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (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	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	5 / 18 (27.78%)	
Gastrointestinal disorders			
Nausea/Vomiting			
subjects affected / exposed	6 / 17 (35.29%)	5 / 18 (27.78%)	
occurrences (all)	6	5	

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