Clinical trial results:
Perioperativ installation of ropivacain in mastectomy – with or without axillary lymph node dissection after sentinel node diagnostics or known lymph node metastasis – A double-blind, randomized clinical trial of the effect on postoperative pain

Summary

EudraCT number	2012-001557-46
Trial protocol	DK
Global end of trial date	01 September 2018

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	The Good Clinical Practice Unit - Odense: 12.005, Danish Medicines Agency: LMST2012053739, The Regional Committees on Health Research Ethics : S-20120095, The Danish Data Protection Agency: 2012-001557-46

Notes:

Sponsors

Sponsor organisation name	Odense Universityhospital
Sponsor organisation address	Sdr. Boulevard 25, Odense C, Denmark, 5000
Public contact	Søren Rune Larsen, Odense Universitetshospital, Department of Anesthesiology and Intensive Care Medicine, +45 65412063, soeren.rune.larsen@rsyd.dk
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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	29 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2018
Global end of trial reached?	Yes
Global end of trial date	01 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect on pain relief, after installation of ropivacaine with adrenaline in unilateral mastectomy with or without axillary lymph node dissection, at the end of the operation.
The effect is rated via VAS-score (Visual Analogue Scale) an modified VAS-score

Protection of trial subjects:

Close observation by Anestehetic personal and postoperativecare nurses, and monitoring of vital signs parametres.

Background therapy:

Standard treatment beside study drug

Evidence for comparator:

Ropivacaine compared to placebo (Isotonic Saline)

Actual start date of recruitment	23 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	19
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult females undergoing unilateral mastectomy with or without axillary lymph node dissection after sentinel lymph node biopsy or known lymph node metastases at the Hospital of South West Jutland (located in Esbjerg - Denmark). In the period from June 2012 to December 2014

Pre-assignment

Screening details:

Evaluation by anesthesiologist

Period 1

Period 1 title	Overall 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:

Installation of Ropivacaine

Arm type	Experimental
Investigational medicinal product name	Ropivacain "Fresenius Kabi": 2 mg/ml
Investigational medicinal product code	i
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use, Subdermal use

Dosage and administration details:

Installation of 100 ml Ropivacaine 2 mg/ml added adrenaline to a concentration of 2 µg/ml into the mastectomy cavity .

Arm title	Placebo

Arm description:

Installation of isotonic saline to the mastectomy cavity

Arm type	Placebo
Investigational medicinal product name	Natriumklorid 9 mg/ml "Fresenius Kabi"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use, Subdermal use

Dosage and administration details:

100 ml of Natriumklorid 9 mg/ml added adrenaline to a concentration of 2 µg/ml installed into the mastectomy cavity.

Number of subjects in period 1	Active	Placebo
Started	17	13
Completed	17	13

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description: Installation of Ropivacaine	
Reporting group title	Placebo
Reporting group description: Installation of isotonic saline to the mastectomy cavity	

Reporting group values	Active	Placebo	Total
Number of subjects	17	13	30
Age categorical Units: Subjects			
Adults (18-64 years)	10	9	19
From 65-84 years	7	4	11
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	17	13	30
Male	0	0	0
Smoker Units: Subjects			
Smoker	4	3	7
Non-Smoker	9	9	18
Former Smoker	4	1	5
PONV			
Previous PostOperative Nausea or Vomiting			
Units: Subjects			
Yes	1	3	4
No	16	10	26
Motion sickness			
Tendency to Motion Sickness			
Units: Subjects			
Yes	4	3	7
No	12	9	21
Not Done	1	1	2
Allergies Units: Subjects			
Food	1	1	2
Medicine	2	3	5
Non	14	9	23
Type of Surgery			
Unilateral mastectomy with or without axillary lymph node dissection			
Units: Subjects			
With axillary lymph node dissection	6	6	12
Without axillary lymph node dissection	11	7	18
History of pain			

Does the patient have a history of ongoing pain up to surgery.

Comorbidity - Depression Disorder			
Units: Subjects			
Yes	1	0	1
No	16	13	29

End points

End points reporting groups

Reporting group title	Active
Reporting group description: Installation of Ropivacaine	
Reporting group title	Placebo
Reporting group description: Installation of isotonic saline to the mastectomy cavity	

Primary: Pain assesment postoperatively

End point title	Pain assesment postoperatively
End point description: To investigate the effect on pain relief, after installation of ropivacaine with adrenaline in unilateral mastectomy with or without axillary lymph node dissection, at the end of the operation. The effect is rated via median VAS-score (VisualAnalogue Scale) for all measurements in each group.	
End point type	Primary
End point timeframe: Postoperatively from arriving at the PACU untill 24 hours postoperatively	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: VAS				
number (not applicable)	1.63	1.46		

Statistical analyses

Statistical analysis title	Wilcoxon non parametric test
Comparison groups	Active v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.99
Method	Wilcoxon (Mann-Whitney)

Secondary: Postoperative use of analgesia

End point title	Postoperative use of analgesia
End point description: To investigate the postoperatively use of opioid (morphine equivalents in mg), after installation of	

ropivacaine with adrenaline in unilateral mastectomy with or without axillary lymph node dissection.
The effect is rated via median administrated amounts of morphine equivalents in mg in each group.

End point type	Secondary

End point timeframe:

Postoperatively from arriving at the PACU untill 24 hours postoperatively

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: Mg				
number (not applicable)	16	44		

Statistical analyses

Statistical analysis title	Wilcoxon non parametric test
Comparison groups	Active v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0804
Method	Wilcoxon (Mann-Whitney)

Secondary: Effect on PONV (Postoperative nausea and vomiting)

End point title	Effect on PONV (Postoperative nausea and vomiting)

End point description:

To investigate the effect on PONV (Postoperative Nausea and Vomiting) after installation of ropivacaine with adrenaline in unilateral mastectomy with or without axillary lymph node dissection, at the end of the operation.
The effect is rated via median of all measured VAS-score (VisualAnalogue Scale) in each group.
Analyzed as yes or no

End point type	Secondary

End point timeframe:

Postoperatively from arriving at the PACU untill 24 hours postoperatively

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: Yes or No				
Yes	4	3		
No	13	10		

Statistical analyses

Statistical analysis title	Fishers exact test
Comparison groups	Active v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.66
Method	Fisher exact

Secondary: Use of antiemetic

End point title	Use of antiemetic

End point description:

To investigate the use of antiemetics after installation of ropivacaine with adrenaline in unilateral mastectomy with or without axillary lymph node dissection, at the end of the operation.
The effect is rated via mean of the converting antiemetic factor (as described by the antiemetic equivalences table in the protocol) in each group.
Then recorded as yes or no

End point type	Secondary

End point timeframe:

Postoperatively from arriving at the PACU untill 24 hours postoperatively

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: Yes or No				
Yes	1	1		
No	16	12		

Statistical analyses

Statistical analysis title	Fishers exact test
Comparison groups	Placebo v Active

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.687
Method	Fisher exact

Secondary: Length of hospital stay	
End point title	Length of hospital stay
End point description: The effect is rated via median length of hospital stay in minutes in each group.	
End point type	Secondary
End point timeframe: Postoperatively from arriving at the PACU untill discharge from hospital	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: minute				
number (not applicable)	2805	2713		

Statistical analyses

Statistical analysis title	Wilcoxon non parametric test
Comparison groups	Active v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8691
Method	Wilcoxon (Mann-Whitney)

Secondary: Time till first mobilisation	
End point title	Time till first mobilisation
End point description: The effect is rated via median Time till first mobilisation in minutes in each group.	
End point type	Secondary
End point timeframe: Postoperatively from arriving at the PACU untill first mobilisation	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: minute				
number (not applicable)	100	130		

Statistical analyses

Statistical analysis title	Wilcoxon non parametric test
Comparison groups	Active v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.406
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Yearly report to the Danish authorites.

Adverse event reporting additional description:

All Adverse Events is registred emidently in the CRF and reported to the Danish authorites in the yearly report of Adverse Events.
All Serious Adverse Events is registred emidently in the CRF and reported to the Danish authorites within the first 24 hours.
No Adverse Events or Serious Adverse Events has occurred in the study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Because the procedure is a low risk procedure, where installation is done through the existing surgical drain, and only half of the expected numbers of patients has gone through the study, no adverse event and no non-serious adverse event has occurred.

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
01 September 2018	Trial has been terminated early due to lack of patients going through mastectomy at the trial site in Esbjerg. Through the last 2 years of the trial periode, there were not included any contestants to the trial. As it was not possible to include a other trial site, it was decided to terminate the trial early.	-

Notes:

Limitations and caveats

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

Trial has been terminated early due to lack of patients going through mastectomy at the trial site in Esbjerg, leading to a smaller number of subjects analysed.

Notes: