Clinical trial results:
The DESIGN trial : A randomised, Double-blind, placEbo-controlled Study to assess the effectIveness of pectoral nerves block (Pecs) after breast surGery on Piritramide coNsumption.

Summary

EudraCT number	2015-005574-38
Trial protocol	BE
Global end of trial date	11 January 2022

Results information

Result version number	v1 (current)
This version publication date	17 March 2022
First version publication date	17 March 2022
Summary attachment (see zip file)	Summary (DESIGN_Final_study_report.pdf)

Trial information

Trial identification

Sponsor protocol code	IJB-SUR-DESIGN-2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02655965
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Jules Bordet
Sponsor organisation address	Rue Meylemeersch,90, Brussels, Belgium, 1070
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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	11 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2021
Global end of trial reached?	Yes
Global end of trial date	11 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effectiveness of pecs block associated to a general anaesthesia in terms of total Piritramide consumption.

Protection of trial subjects:

Throughout the study the dedicated sponsor study team members verified the data to ensure that:
- the rights and well-being of subjects were protected
- the reported trial data were accurate, complete and verifiable from source documents
- the conduct of the trial was compliant with the IHC-GCP, the applicable regulatory requirements, the study protocol and the study guidelines
Quality control activities combined central monitoring and clinical site monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 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: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	45
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

57 subjects were registered and randomised in the DESIGN trial:
- 28 were randomised in the intervention arm: ropivacaine 3.5 mg/ml + clonidine 5 µg/ml
- 29 were randomised in the control arm (NaCl 0.9%)

Pre-assignment

Screening details:

Subjects will only be eligible for study participation if they meet all the following inclusion criteria. Subjects who exhibit any of the following conditions at screening will not be eligible for admission into the study.

Pre-assignment period milestones

Number of subjects started	57
Number of subjects completed	57

Period 1

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

Blinding implementation details:

Both treatments were be labelled by the pharmacist using a unique treatment identification code to ensure blinding of treatment. The active and placebo preparations were identical and presented in the same packaging to ensure blinding of the study medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A : Intervention arm

Arm description:

10 ml of Ropivacaine 3.5 mg/ml and Clonidine 5 µg/ml injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior

Arm type	Experimental
Investigational medicinal product name	Ropivacaine
Investigational medicinal product code	
Other name	ropivacaine hydrochloride monohydrate
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

10 ml of 3.5 mg/ml injected between pectoral muscles

Investigational medicinal product name	Clonidine
Investigational medicinal product code	
Other name	clonidine hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

20 ml of 5 µg/ml between the muscles pectoralis minor and serratus anterior.

Arm title	Arm B : Control arm

Arm description:

10 ml of placebo (sodium chloride 0.9% (NaCl 0.9%)) injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior

Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9% (NaCl 0.9%)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

1000 ml solution for injection contains 9 g of sodium chloride
All subjects randomised in the Placebo arm will be injected (perineural use) with a solution of 10 ml of NaCl 0.9% between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior

Number of subjects in period 1	Arm A : Intervention arm	Arm B : Control arm
Started	28	29
Completed	27	28
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A : Intervention arm
Reporting group description:	
10 ml of Ropivacaine 3.5 mg/ml and Clonidine 5 µg/ml injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior	
Reporting group title	Arm B : Control arm
Reporting group description:	
10 ml of placebo (sodium chloride 0.9% (NaCl 0.9%)) injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior	

Reporting group values	Arm A : Intervention arm	Arm B : Control arm	Total
Number of subjects	28	29	57
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)	22	23	45
From 65-84 years	6	6	12
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	28	29	57
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm A : Intervention arm
Reporting group description:	
10 ml of Ropivacaine 3.5 mg/ml and Clonidine 5 µg/ml injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior	
Reporting group title	Arm B : Control arm
Reporting group description:	
10 ml of placebo (sodium chloride 0.9% (NaCl 0.9%)) injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior	

Primary: Piritramide consumption at 24 hours postoperatively

End point title	Piritramide consumption at 24 hours postoperatively[1]
End point description:	
End point type	Primary
End point timeframe:	
24 hours postoperatively	

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: The distributions of Piritramide consumption will be compared using a non-parametric test for location

End point values	Arm A : Intervention arm	Arm B : Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	27		
Units: mg				
median (inter-quartile range (Q1-Q3))	6 (4 to 13)	8 (2 to 14)		

Attachments (see zip file)	Boxplot/1.PNG Histogram.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic pain intensity at 6 months post-surgery

End point title	Chronic pain intensity at 6 months post-surgery
End point description:	

Score obtained on the Mc Gill Pain questionnaire (SF-MPQ 2). The short form of the McGill Pain Questionnaire (SF-MPQ 2) consists of 22 descriptors (6 items related to continuous pain, 6 items related to intermittent pain, 8 items related to neuropathic pain and 4 items related to affective) which are rated on an intensity scale as 0 “no pain” to 10 “worst pain”.

End point type	Secondary

End point timeframe:

all eligible patients, treated and without heavy surgery during the 6 months follow-up, having adequately filled the Mc Gill questionnaire will be analysed for this endpoint. Distributions of the overall score will be compared using a non-parametric

End point values	Arm A : Intervention arm	Arm B : Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: result				
median (inter-quartile range (Q1-Q3))	0.5 (0.3 to 1.0)	0.5 (0.1 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Present pain intensity until 48 hours post-surgery at rest

End point title	Present pain intensity until 48 hours post-surgery at rest

End point description:

Present pain intensity post-surgery will be measured using VAS score (1–10).

The pain VAS is a single-item scale. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10)

End point type	Secondary

End point timeframe:

at rest : T0, 30 min, 1hr, 1h30, 2hrs, 4 hrs, 6 hrs, 8 hrs, 24 hrs, 32hrs, 48 hrs post surgery

End point values	Arm A : Intervention arm	Arm B : Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: AUC				
median (inter-quartile range (Q1-Q3))	23 (0 to 134)	24 (0 to 177)		

Statistical analyses

No statistical analyses for this end point

Secondary: Present pain intensity until 48 hours post-surgery during movement

End point title	Present pain intensity until 48 hours post-surgery during movement

End point description:

End point type	Secondary

End point timeframe:

during movement : 2hrs, 4 hrs, 6 hrs, 8 hrs, 24 hrs, 32hrs, 48 hrs post surgery

End point values	Arm A : Intervention arm	Arm B : Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: AUC				
median (inter-quartile range (Q1-Q3))	63 (0 to 177)	45 (12 to 149)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent (IC) signature until 3 days after the last administration of study treatment, all AEs should be reported on the AE page of the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Arm A : Intervention arm

Reporting group description:

10 ml of Ropivacaine 3.5 mg/ml and Clonidine 5 µg/ml injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior

Reporting group title	Arm B : Control arm

Reporting group description:

10 ml of placebo (sodium chloride 0.9% (NaCl 0.9%)) injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior

Serious adverse events	Arm A : Intervention arm	Arm B : Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (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	Arm A : Intervention arm	Arm B : Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 27 (51.85%)	24 / 28 (85.71%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 27 (3.70%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Seroma			
subjects affected / exposed	4 / 27 (14.81%)	3 / 28 (10.71%)	
occurrences (all)	4	3	
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 27 (3.70%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	9 / 27 (33.33%)	17 / 28 (60.71%)	
occurrences (all)	9	17	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Post procedural infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2016	- VAS assessments changes - Adding one exclusion criteria: subjects that require bilateral mastectomy or bilateral lumpectomy
23 October 2017	- Inclusion and exclusion criteria clarification (Adequate liver function and cardiac function assessment) - Length of study (recruitment period)
14 November 2018	ICF amendment due to changes in European Data Privacy legislative framework
03 December 2018	Sample size modification

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.

Due to slow accrual, the sample size has been modified (protocol version 4.0): targeting a statistical power of 0.80 instead of 0.90

Notes: