Clinical trial results:
Does preperitoneal local anesthesia in laparoscopic gastric bypass surgery reduce postoperative pain and opioid consumption?

Summary

EudraCT number	2012-002618-38
Trial protocol	NL
Global end of trial date	01 October 2015

Results information

Result version number	v1 (current)
This version publication date	23 September 2017
First version publication date	23 September 2017

Trial information

Trial identification

Sponsor protocol code	AnesBar01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Rijnstate Hospital, department of Anesthesia
Sponsor organisation address	Wagnerlaan 55, Arnhem, Netherlands,
Public contact	Dr. E.T. Kamphuis, anesthesiologist, Rijnstate Hospital, department of Anesthesia, +31 0880058888, ekamphuis@rijnstate.nl
Scientific contact	Dr. E.T. Kamphuis, anesthesiologist, Rijnstate Hospital, department of Anesthesia, +31 0880058888,

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	07 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2015
Global end of trial reached?	Yes
Global end of trial date	01 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the postoperative opioid consumption and pain after laparoscopic bariatric surgery. Our hypothesis is that less opioids will be consumed by patients in the group receiving local anesthetics compared to normal saline.

Protection of trial subjects:

As this is a trial of analgesics, an escape plan for postoperative pain was in place to make sure patients would not suffer from more pain than to be expected after such a procedure.

Background therapy:

Patients received the usual analgesic and anti-emetic medication alongside the intervention.
At the recovery:
− NRS > 3 and/or when the patient tells he needs more analgesics: morfine 2.5mg IV
− Antihypertensive medication: clonidine 75 micrograms
− Anti-emetics: ondansetron 4mg, droperidol 1.25mg IV. Anti-emetics will be given on demand of the patient.
At the ward:
− Paracetamol 4dd 1000mg per os
− Morfine 10mg subcutaneous injection at the day of surgery or tramadol 50mg the day(s) after surgery: when the patient tells he needs more analgesics. There will be a minimum of one hour between gifts of analgesics and nurses will test if patients are not too sedated to make sure a patient does not get an overdose.
− Anti-emetics: ondansetron 4mg, droperidol 1.25mg, metoclopramid 20mg iv. Anti-emetics will be given on demand of the patient.

Evidence for comparator:

Normal saline is used as a comparator. This has no analgesic effects.

Actual start date of recruitment	21 May 2014
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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recuitment took place from 21/05/2014-15/07/2014 at the Rijnstate Hospital in Arnhem, the Netherlands

Pre-assignment

Screening details:

201 patients were screened.
Exclusion of patients:
- No informed consent: 48
- More extensive surgery: 35
- Chronic pain patients: 15
- Morphine intolerance: 3

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, Carer, Assessor

Blinding implementation details:

Medication was packaged in normal 20ml syringes with a label saying "bupivacaine/placebo" for every patient. It was not possible to distinguish one from the other. The randomisation code was not broken until the last patient had had their last visit in our hospital.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bupivacaine

Arm description:

Patients receiving investigational product

Arm type	Experimental
Investigational medicinal product name	Bupivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion, Injection
Routes of administration	Infiltration

Dosage and administration details:

Bupivacaine 5mg/ml, a total of 30-40ml by pre peritoneal at the incision ports of surgery

Arm title	Placebo

Arm description:

Patients receiving normal saline as a placebo

Arm type	Placebo
Investigational medicinal product name	Normal saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Infiltration

Dosage and administration details:

Normal saline, NaCl 0.9%, injected 30-40ml pre peritoneal at the incision ports of surgery

Number of subjects in period 1	Bupivacaine	Placebo
Started	50	50
Completed	48	48
Not completed	2	2
No surgery at all	1	-
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Bupivacaine
Reporting group description:	
Patients receiving investigational product	
Reporting group title	Placebo
Reporting group description:	
Patients receiving normal saline as a placebo	

Reporting group values	Bupivacaine	Placebo	Total
Number of subjects	50	50	100
Age categorical			
Units: Subjects			
Adults (18-64 years)	50	50	100
From 65-84 years	0	0	0
Age continuous			
Units: years			
geometric mean	45.2	44.8	
standard deviation	± 10	± 11.1	-
Gender categorical			
Units: Subjects			
Female	36	38	74
Male	12	9	21
Not recorded	2	3	5
ASA classification			
Classification used in anaesthesia to assess a global idea of patients' health. ASA 1: healthy patient ASA 2: patient with a mild systemic disease ASA 3: patient with a severe systemic disease ASA 4: patient with a severe systemic disease that is a constant threat to life ASA 5: a moribund patient who is not expected to survive without the operation			
Units: Subjects			
ASA 1	5	7	12
ASA 2	41	37	78
ASA 3	2	3	5
ASA 4	0	0	0
ASA 5	0	0	0
Not recorded	2	3	5
Chronic pain in past			
Whether patients had experienced chronic pain in the past. Defined by using opioids for a longer period of time and being treated by a pain specialist.			
Units: Subjects			
Yes	19	25	44
No	29	22	51
Not recorded	2	3	5
Abdominal surgery in the past			
Units: Subjects			
Yes	27	23	50
No	21	24	45

Not recorded	2	3	5
Type of surgery Units: Subjects			
Laparoscopic sleeve gastrectomy	2	3	5
Laparoscopic gastric bypass	46	44	90
Not recorded	2	3	5
Weight Units: Kg			
geometric mean	125.6	128.5	
standard deviation	± 18.7	± 20.5	-
Height Units: Meters			
geometric mean	171	170	
standard deviation	± 8.8	± 8.1	-
Body Mass Index Units: kg/m2			
geometric mean	42.8	44.5	
standard deviation	± 5	± 5.8	-
Studymedication			
The amount of study medication given in milliliters			
Units: millilitres			
median	37	39	
inter-quartile range (Q1-Q3)	36 to 40	35 to 40	-
Duration of surgery Units: Minutes			
geometric mean	49.3	50.9	
standard deviation	± 14.6	± 17.26	-

End points

End points reporting groups

Reporting group title	Bupivacaine
Reporting group description: Patients receiving investigational product	
Reporting group title	Placebo
Reporting group description: Patients receiving normal saline as a placebo	

Primary: Morphine at the recovery in mg

End point title	Morphine at the recovery in mg
End point description:	
End point type	Primary
End point timeframe: During time spent at the recovery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	2.5 (0 to 5)	5 (2.5 to 7.5)		

Statistical analyses

Statistical analysis title	Analysis of morphine use at the recovery
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Wilcoxon (Mann-Whitney)

Primary: Morphine at the ward in mg

End point title	Morphine at the ward in mg
End point description:	
End point type	Primary

End point timeframe:
In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Analysis of morphine use at the ward
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Wilcoxon (Mann-Whitney)

Primary: Tramadol use at the ward in mg

End point title	Tramadol use at the ward in mg

End point description:

End point type	Primary

End point timeframe:
In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	0 (0 to 10)	0 (0 to 10)		

Statistical analyses

Statistical analysis title	Analysis of tramadol use at the ward
Comparison groups	Bupivacaine v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Wilcoxon (Mann-Whitney)

Primary: Preoperative pain, at the preoperative policlinic

End point title	Preoperative pain, at the preoperative policlinic

End point description:

End point type	Primary

End point timeframe:

Pain before surgery, at the policlinic, at rest

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
geometric mean (standard error)	1.15 (± 0.24)	1.89 (± 0.24)		

Attachments (see zip file)	Pain at rest /Figure 2A.jpg

Statistical analyses

Statistical analysis title	Analysis pain at the policlinic
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Primary: Postoperative pain, right before surgery

End point title	Postoperative pain, right before surgery

End point description:

End point type	Primary

End point timeframe:

Pain at the holding area, right before surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
geometric mean (standard error)	0.19 (± 0.24)	0.43 (± 0.24)		

Statistical analyses

Statistical analysis title	Analysis of pain
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=0, arrival at the recovery

End point title	Pain at T=0, arrival at the recovery

End point description:

End point type	Primary

End point timeframe:

Pain at arrival at the recovery after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[1]	47		
Units: 10				
geometric mean (standard error)	3.43 (± 0.24)	4.32 (± 0.24)		

Notes:

[1] - 1 missing patient

Statistical analyses

Statistical analysis title	Analysis of pain
Comparison groups	Bupivacaine v Placebo

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=15, 15min after arrival at the recovery

End point title	Pain at T=15, 15min after arrival at the recovery

End point description:

End point type	Primary

End point timeframe:

15 min after arrival at the recovery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
geometric mean (standard error)	4.33 (± 0.24)	5.53 (± 0.24)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=15
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=30, 30 min after surgery at arrival at the recovery

End point title	Pain at T=30, 30 min after surgery at arrival at the recovery

End point description:

End point type	Primary

End point timeframe:

30 min after surgery at the recovery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
geometric mean (standard error)	4.33 (± 0.24)	5.6 (± 0.24)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=30
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=45, 45 min after arrival at the recovery

End point title	Pain at T=45, 45 min after arrival at the recovery

End point description:

End point type	Primary

End point timeframe:

45min after arrival at the recovery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: 10				
geometric mean (standard error)	3.98 (± 0.24)	5.14 (± 0.24)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=45
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=60, 60min after arrival at the recovery	
End point title	Pain at T=60, 60min after arrival at the recovery
End point description:	

End point type	Primary
End point timeframe:	
60min after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: 10				
geometric mean (standard error)	3.65 (± 0.25)	4.52 (± 0.25)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=60
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=2, at rest	
End point title	Pain at T=2, at rest
End point description:	

End point type	Primary
End point timeframe:	
2 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42		
Units: 10				
geometric mean (standard error)	3.76 (± 0.24)	4.06 (± 0.25)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=2
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=2, at movement/mobilisation

End point title	Pain at T=2, at movement/mobilisation

End point description:

End point type	Primary

End point timeframe:

2 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: 10				
geometric mean (standard error)	3.94 (± 0.21)	4.24 (± 0.21)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=2, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=4, at rest	
End point title	Pain at T=4, at rest
End point description:	

End point type	Primary
End point timeframe:	
4 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: 10				
geometric mean (standard error)	3.17 (± 0.24)	3.51 (± 0.25)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=4, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=4, at movement/mobilisation	
End point title	Pain at T=4, at movement/mobilisation
End point description:	

End point type	Primary
End point timeframe:	
4 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: 10				
geometric mean (standard error)	3.26 (± 0.21)	3.84 (± 0.21)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=4, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=6, at rest

End point title	Pain at T=6, at rest

End point description:

End point type	Primary

End point timeframe:

6 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: 10				
geometric mean (standard error)	3.02 (± 0.25)	3.35 (± 0.25)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=6, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=6, at mobilisation

End point title	Pain at T=6, at mobilisation

End point description:

End point type	Primary

End point timeframe:

6 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: 10				
geometric mean (standard error)	3.1 (± 0.21)	3.73 (± 0.21)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=6,mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=8, at rest

End point title	Pain at T=8, at rest

End point description:

End point type	Primary

End point timeframe:

8 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: 10				
geometric mean (standard error)	2.87 (± 0.25)	3.09 (± 0.26)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=8, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=8, at mobilisation

End point title	Pain at T=8, at mobilisation

End point description:

End point type	Primary

End point timeframe:

8 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: 10				
geometric mean (standard error)	3.26 (± 0.21)	3.16 (± 0.21)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=8, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=10, at rest	
End point title	Pain at T=10, at rest
End point description:	

End point type	Primary
End point timeframe:	
10 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: 10				
geometric mean (standard error)	2.5 (± 0.26)	3 (± 0.26)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=10, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=10, at mobilisation	
End point title	Pain at T=10, at mobilisation
End point description:	

End point type	Primary
End point timeframe:	
10 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: 10				
geometric mean (standard error)	3.01 (± 0.22)	3.31 (± 0.22)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=10, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=12, at rest

End point title	Pain at T=12, at rest

End point description:

End point type	Primary

End point timeframe:

12 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	33		
Units: 10				
geometric mean (standard error)	2.9 (± 0.26)	3.11 (± 0.28)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=12, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=12, at mobilisation	
End point title	Pain at T=12, at mobilisation
End point description:	

End point type	Primary
End point timeframe:	
12 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	30		
Units: 10				
geometric mean (standard error)	3.22 (± 0.22)	3.28 (± 0.24)		

Statistical analyses

Statistical analysis title	Analysis of pain at T=12, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=14, at rest	
End point title	Pain at T=14, at rest
End point description:	

End point type	Primary
End point timeframe:	
14 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: 10				
geometric mean (standard error)	2.78 (± 0.25)	2.96 (± 0.26)		

Statistical analyses

Statistical analysis title	Pain at T=14, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=14, at mobilisation

End point title	Pain at T=14, at mobilisation

End point description:

End point type	Primary

End point timeframe:

14 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: 10				
geometric mean (standard error)	3.11 (± 0.22)	3.24 (± 0.22)		

Statistical analyses

Statistical analysis title	Pain at T=14, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=16, at rest	
End point title	Pain at T=16, at rest
End point description:	

End point type	Primary
End point timeframe:	
16 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: 10				
geometric mean (standard error)	2.8 (± 0.24)	2.99 (± 0.25)		

Statistical analyses

Statistical analysis title	Pain at T=16, at rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=16, at mobilisation	
End point title	Pain at T=16, at mobilisation
End point description:	

End point type	Primary
End point timeframe:	
16 hours after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: 10				
geometric mean (standard error)	2.99 (± 0.21)	3.23 (± 0.21)		

Statistical analyses

Statistical analysis title	Pain at T=16, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=18, at rest

End point title	Pain at T=18, at rest

End point description:

End point type	Primary

End point timeframe:

18 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	43		
Units: 10				
geometric mean (standard error)	2.65 (± 0.24)	2.91 (± 0.25)		

Statistical analyses

Statistical analysis title	Pain at T=18, at rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=18, at mobilisation

End point title	Pain at T=18, at mobilisation

End point description:

End point type	Primary

End point timeframe:

18 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	42		
Units: 10				
geometric mean (standard error)	2.79 (± 0.2)	3.25 (± 0.21)		

Statistical analyses

Statistical analysis title	Pain at T=18, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=20, at rest

End point title	Pain at T=20, at rest

End point description:

End point type	Primary

End point timeframe:

20 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
geometric mean (standard error)	2.38 (± 0.24)	2.72 (± 0.24)		

Statistical analyses

Statistical analysis title	Pain at T=20, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=20, at mobilisation

End point title	Pain at T=20, at mobilisation

End point description:

End point type	Primary

End point timeframe:

20 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: 10				
geometric mean (standard error)	2.63 (± 0.2)	3.1 (± 0.2)		

Statistical analyses

Statistical analysis title	Pain at T=20, mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=22, at rest

End point title	Pain at T=22, at rest

End point description:

End point type	Primary

End point timeframe:

22 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: 10				
geometric mean (standard error)	2.32 (± 0.24)	2.46 (± 0.24)		

Statistical analyses

Statistical analysis title	Pain at T=22, rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=22, at mobilisation

End point title	Pain at T=22, at mobilisation

End point description:

End point type	Primary

End point timeframe:

22 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: 10				
geometric mean (standard error)	2.62 (± 0.2)	2.85 (± 0.21)		

Statistical analyses

Statistical analysis title	Pain at T=22, at mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=24, at rest

End point title	Pain at T=24, at rest

End point description:

End point type	Primary

End point timeframe:

24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: 10				
geometric mean (standard error)	2.15 (± 0.24)	2.39 (± 0.24)		

Statistical analyses

Statistical analysis title	Pain at T=24, at rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Wilcoxon (Mann-Whitney)

Primary: Pain at T=24, at mobilisation

End point title	Pain at T=24, at mobilisation

End point description:

End point type	Primary

End point timeframe:

24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: 10				
geometric mean (standard error)	2.46 (± 0.2)	2.65 (± 0.21)		

Statistical analyses

Statistical analysis title	Pain at T=24, at mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Wilcoxon (Mann-Whitney)

Secondary: Clonidine at recovery in ug

End point title	Clonidine at recovery in ug

End point description:

End point type	Secondary

End point timeframe:

During time spent at the recovery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	0 (0 to 75)	0 (0 to 113)		

Statistical analyses

Statistical analysis title	Analysis of clonidine use at the recovery
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to rescue medication in minutes

End point title	Time to rescue medication in minutes

End point description:

End point type	Secondary

End point timeframe:

In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	21 (14 to 28)	19 (9 to 28)		

Statistical analyses

Statistical analysis title	Analysis of time to rescue medication
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Wilcoxon (Mann-Whitney)

Secondary: Opioids needed

End point title	Opioids needed

End point description:

End point type	Secondary

End point timeframe:

In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	34	38		
No	14	9		

Statistical analyses

Statistical analysis title	Analysis of opioids needed or not
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Fisher exact

Secondary: Rescue medication needed

End point title	Rescue medication needed

End point description:

End point type	Secondary

End point timeframe:

In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	35	40		
No	13	7		

Statistical analyses

Statistical analysis title	Analysis of rescue medication needed or not
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Fisher exact

Secondary: Extra antiemetic's needed

End point title	Extra antiemetic's needed

End point description:

End point type	Secondary

End point timeframe:

In the first 24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	20	25		
No	28	22		

Statistical analyses

Statistical analysis title	Analysis of extra antiemetic's needed or not
Comparison groups	Bupivacaine v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Fisher exact

Secondary: Mobilisation possible within two hours

End point title	Mobilisation possible within two hours

End point description:

End point type	Secondary

End point timeframe:

Within 2 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	41	42		
No	3	4		
Not recorded	4	1		

Statistical analyses

Statistical analysis title	Analysis of mobilisation possible
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Trouble falling asleep

End point title	Trouble falling asleep

End point description:

End point type	Secondary

End point timeframe:

First night after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	14	24		
No	34	23		

Statistical analyses

Statistical analysis title	Analysis of trouble falling asleep
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact

Secondary: Waking up because of pain

End point title	Waking up because of pain

End point description:

End point type	Secondary

End point timeframe:

First night after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 100				
Yes	19	24		
No	29	23		

Statistical analyses

Statistical analysis title	Analysis of waking up because of pain
Comparison groups	Bupivacaine v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Fisher exact

Secondary: Satisfaction with pain treatment

End point title	Satisfaction with pain treatment

End point description:

End point type	Secondary

End point timeframe:

24 hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
median (inter-quartile range (Q1-Q3))	8 (7 to 10)	8 (7 to 9)		

Statistical analyses

Statistical analysis title	Analysis of satisfaction with pain treatment
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of stay, recovery (minutes)

End point title	Duration of stay, recovery (minutes)

End point description:

End point type	Secondary

End point timeframe:

First hours after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 200				
median (inter-quartile range (Q1-Q3))	92 (82 to 106)	101 (89 to 120)		

Statistical analyses

Statistical analysis title	Analysis of duration of stay, recovery
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of stay in the hospital (days)

End point title	Duration of stay in the hospital (days)

End point description:

End point type	Secondary

End point timeframe:

Days after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: 10				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Analysis of duration of stay, hospital stay
Comparison groups	Bupivacaine v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain after surgery

End point title	Pain after surgery

End point description:

End point type	Secondary

End point timeframe:

One year after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: 100				
Much less	17	8		
Less	8	11		
Same	16	20		
More	4	5		
Much more	0	3		

Statistical analyses

Statistical analysis title	Analysis of change in pain after surgery
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Secondary: Effect of pain on daily activities

End point title	Effect of pain on daily activities

End point description:

End point type	Secondary

End point timeframe:

One year after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: 10				
Much less	15	7		
Less	11	9		
Same	16	22		
More	2	8		
Much more	0	1		

Statistical analyses

Statistical analysis title	Analysis of effect on daily living
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Fisher exact

Secondary: Change in use of painkillers

End point title	Change in use of painkillers
End point description:	
Change in use of painkillers as reported by the patients themselves.	
End point type	Secondary
End point timeframe:	
One year after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: 10				
Much less	7	2		
Less	12	12		
Same	25	25		
More	1	8		
Much more	0	0		

Statistical analyses

Statistical analysis title	Analysis of change in use of painkillers
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Fisher exact

Secondary: Pain at T=2wk, at rest	
End point title	Pain at T=2wk, at rest
End point description:	
End point type	Secondary
End point timeframe:	
2 weeks after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: 10				
geometric mean (standard error)	0.08 (± 0.25)	0.28 (± 0.25)		

Statistical analyses

Statistical analysis title	Pain at T=2wk, at rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain at T=2wk, at mobilisation	
End point title	Pain at T=2wk, at mobilisation
End point description:	

End point type	Secondary
End point timeframe:	
2 weeks after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: 10				
geometric mean (standard error)	0.11 (± 0.21)	0.24 (± 0.21)		

Statistical analyses

Statistical analysis title	Pain at T=2wk, at mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain at T=6wk, at rest	
End point title	Pain at T=6wk, at rest
End point description:	

End point type	Secondary
End point timeframe:	
6 weeks after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	29		
Units: 10				
geometric mean (standard error)	0.002 (± 0.28)	0.24 (± 0.29)		

Statistical analyses

Statistical analysis title	Pain at T=6wk, at rest
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain at T=6wk, at mobilisation

End point title	Pain at T=6wk, at mobilisation
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks after surgery	

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: 10				
geometric mean (standard error)	0.04 (± 0.23)	0.09 (± 0.24)		

Statistical analyses

Statistical analysis title	Pain at T=6wk, at mobilisation
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain one year after surgery

End point title	Pain one year after surgery

End point description:

End point type	Secondary

End point timeframe:

Pain on a numeric rating scale one year after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: 10				
geometric mean (standard deviation)	1.36 (± 2.2)	2.7 (± 2.8)		

Statistical analyses

Statistical analysis title	Pain one year after surgery
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Secondary: Prevalence NRS >4

End point title	Prevalence NRS >4

End point description:

End point type	Secondary

End point timeframe:

1 year after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: 100				
NRS >4	6	19		
NRS <4	32	28		

Statistical analyses

Statistical analysis title	Prevalence NRS >4
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Fisher exact

Secondary: NRS >7

End point title	NRS >7

End point description:

End point type	Secondary

End point timeframe:

1 year after surgery

End point values	Bupivacaine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: 100				
NRS >7	3	6		
NRS <7	42	41		

Statistical analyses

Statistical analysis title	Prevalence NRS >7
Comparison groups	Bupivacaine v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Fisher exact

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

24 hours after surgery

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Placebogroup

Reporting group description: -

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: No non-serious adverse events were recorded during the trial period.

Serious adverse events	Placebogroup		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Re-operation	Additional description: Patient needed reoperation because of postoperative bleeding complication		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebogroup		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		

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