



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: morphine 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
- Morphine 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:

Recruitment 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 | - |
| Study medication | | | |
| 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 (\pm 0.24) | 1.89 (\pm 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 (\pm 0.24) | 0.43 (\pm 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 (\pm 0.24) | 4.32 (\pm 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 (\pm 0.24) | 5.6 (\pm 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 (\pm 0.24) | 5.14 (\pm 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 (\pm 0.24) | 4.06 (\pm 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 (\pm 0.21) | 4.24 (\pm 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 (\pm 0.24) | 3.51 (\pm 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 (\pm 0.21) | 3.84 (\pm 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 (\pm 0.25) | 3.35 (\pm 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 (\pm 0.21) | 3.73 (\pm 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 (\pm 0.25) | 3.09 (\pm 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 (\pm 0.21) | 3.16 (\pm 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 (\pm 0.26) | 3 (\pm 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 (\pm 0.22) | 3.31 (\pm 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 (\pm 0.26) | 3.11 (\pm 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 (\pm 0.22) | 3.28 (\pm 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 (\pm 0.25) | 2.96 (\pm 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 (\pm 0.22) | 3.24 (\pm 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 (\pm 0.21) | 3.23 (\pm 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 (\pm 0.24) | 2.91 (\pm 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 (\pm 0.24) | 2.72 (\pm 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 (\pm 0.2) | 3.1 (\pm 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 (\pm 0.24) | 2.46 (\pm 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 (\pm 0.2) | 2.85 (\pm 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 (\pm 0.24) | 2.39 (\pm 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 (\pm 0.25) | 0.28 (\pm 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