



## Clinical trial results:

### An International, Randomised, Double Blinded, Multi-centre, Active- and Placebo-controlled Dose Response Trial to Evaluate the Efficacy and Safety of SABER-Bupivacaine for Postoperative Pain Control in Patients Following Arthroscopic Shoulder Surgery

#### Summary

EudraCT number	2007-006122-96
Trial protocol	SE AT DE FR LV DK
Global end of trial date	04 February 2011

#### Results information

Result version number	v1 (current)
This version publication date	31 March 2022
First version publication date	31 March 2022

#### Trial information

##### Trial identification

Sponsor protocol code	BU-002-IM
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00993798
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	DURECT Corporation
Sponsor organisation address	10260 Bubb Road, Cupertino, CA, United States, 95014
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 November 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 February 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective is to identify the optimal dose of SABER-Bupivacaine for postoperative pain control administered into the subacromial space in participants undergoing elective arthroscopic shoulder surgery on the basis of pharmacokinetics, efficacy, and safety evaluations.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Latvia: 59
Worldwide total number of subjects	107
EEA total number of subjects	107

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)	99
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study in adult participants undergoing elective arthroscopic shoulder surgery.

### Pre-assignment

Screening details:

Participants were screened 1 to 14 days before surgery at which time informed consent was obtained. Surgery was performed and the study drug was administered on Day 0.

### Period 1

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

Blinding implementation details:

Participants were randomised in a double-blind manner and allocated to one of the three treatment arms in a ratio of 2:1:1. The random allocation of participants into treatment groups was based on a block randomisation list.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	SABER-Bupivacaine

Arm description:

Participants received SABER-Bupivacaine 5.0 millilitre (mL) (600 milligram [mg] bupivacaine) single dose instilled subacromially.

Arm type	Experimental
Investigational medicinal product name	SABER-Bupivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Instillation

Dosage and administration details:

The participant received 9 mL of SABER-Bupivacaine. (132 mg bupivacaine/mL). The correct volume (5 mL in cohort 1) to be administered was drawn at room temperature into a syringe via a 16G (large bore) needle. The needle was then removed and the product was administered within 1 hour of being drawn up into the syringe. The product was administered as a single administration into the subacromial space through one of the arthroscopic portals.

<b>Arm title</b>	SABER-Placebo
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Arm description:

Participants received SABER-Bupivacaine 5.0 mL (placebo) single dose instilled subacromially.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Instillation

Dosage and administration details:

The participant received 9 mL of SABER-placebo. The correct volume (5 mL in cohort 1) to be administered was drawn at room temperature into a syringe via a 16G (large bore) needle. The needle was then removed and the product was administered within 1 hour of being drawn up into the syringe. The product was administered as a single administration into the subacromial space through one of the

arthroscopic portals.

<b>Arm title</b>	Bupivacaine HCl
Arm description: Participants received standard Bupivacaine HCl 20.0 mL (2.5 mg/mL) single dose instilled subacromially.	
Arm type	Active comparator
Investigational medicinal product name	Bupivacaine HCl
Investigational medicinal product code	
Other name	Marcain / Carbostesin
Pharmaceutical forms	Solution for injection
Routes of administration	Infiltration

Dosage and administration details:

Standard bupivacaine HCl 2.5 mg/mL was supplied in vials containing 20 mL of the product (50 mg); the whole vial contents (20 mL) were administered subacromially as a single dose.

<b>Number of subjects in period 1</b>	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Started	53	25	29
Completed	53	25	29

## Baseline characteristics

### Reporting groups

Reporting group title	SABER-Bupivacaine
Reporting group description:	
Participants received SABER-Bupivacaine 5.0 millilitre (mL) (600 milligram [mg] bupivacaine) single dose instilled subacromially.	
Reporting group title	SABER-Placebo
Reporting group description:	
Participants received SABER-Bupivacaine 5.0 mL (placebo) single dose instilled subacromially.	
Reporting group title	Bupivacaine HCl
Reporting group description:	
Participants received standard Bupivacaine HCl 20.0 mL (2.5 mg/mL) single dose instilled subacromially.	

Reporting group values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Number of subjects	53	25	29
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	49	25	25
From 65-84 years	4	0	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	50.1	48.6	51.6
full range (min-max)	28 to 70	24 to 63	21 to 70
Gender categorical			
Units: Subjects			
Female	33	14	17
Male	20	11	12

Reporting group values	Total		
Number of subjects	107		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	99		
From 65-84 years	8		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	64		
Male	43		

## End points

### End points reporting groups

Reporting group title	SABER-Bupivacaine
Reporting group description: Participants received SABER-Bupivacaine 5.0 millilitre (mL) (600 milligram [mg] bupivacaine) single dose instilled subacromially.	
Reporting group title	SABER-Placebo
Reporting group description: Participants received SABER-Bupivacaine 5.0 mL (placebo) single dose instilled subacromially.	
Reporting group title	Bupivacaine HCl
Reporting group description: Participants received standard Bupivacaine HCl 20.0 mL (2.5 mg/mL) single dose instilled subacromially.	

### Primary: Pain Intensity (PI)

End point title	Pain Intensity (PI)
End point description: Mean PI on movement area under the concentration-time curve (AUC) (time-normalized AUC) during the period 0 to 3 days after surgery. Pain intensity was assessed with a standard 0 to 10 numeric rating scale (NRS), where no pain at all was rated as 0 and the worst pain imaginable was rated as 10. The AUC is computed for each participant using the standard trapezoidal rule and normalised by dividing by the time interval over which it is computed. This normalisation converts the AUC to the natural pain scale (NRS 0 to 10) to allow for better translation of the clinical treatment effect magnitude.	
End point type	Primary
End point timeframe: 0 to 3 days after surgery	

End point values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	25	29	
Units: score on a scale (time-normalized AUC)				
arithmetic mean (standard deviation)	5.16 ( $\pm$ 1.94)	6.43 ( $\pm$ 1.77)	5.16 ( $\pm$ 2.38)	

### Statistical analyses

Statistical analysis title	Statistical Analysis for Pain Intensity (PI)
Comparison groups	SABER-Placebo v SABER-Bupivacaine



Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.012
Method	t-test in analysis of variance (ANOVA)
Parameter estimate	Least-square (LS) Mean Difference
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	-0.28
Variability estimate	Standard deviation
Dispersion value	0.5

Notes:

[1] - Exploratory comparison between SABER-Bupivacaine and Bupivacaine HCl was not analyzed inferentially.

### Primary: Supplemental Opioid Use

End point title	Supplemental Opioid Use
End point description:	
Cumulative IV morphine-equivalent dose of opioid rescue medication.	
End point type	Primary
End point timeframe:	
0 to 3 days after surgery	

End point values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	25	29	
Units: mg				
median (inter-quartile range (Q1-Q3))	4.0 (0.0 to 15.0)	12.0 (4.0 to 36.0)	8.0 (0.0 to 16.0)	

### Statistical analyses

Statistical analysis title	Statistical Analysis for Supplemental Opioid Use
Comparison groups	SABER-Bupivacaine v SABER-Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	0

Notes:

[2] - Exploratory comparison between SABER-Bupivacaine and Bupivacaine HCl was not analyzed inferentially.

## Secondary: Time to First Opioid Rescue Medication Usage

End point title	Time to First Opioid Rescue Medication Usage
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End point description:

Time to first opioid rescue medication usage was defined as the duration between time of study drug administration and the time of first opioid use. For participants that did not take any opioids, time to first opioid rescue medication usage was censored and set to time of study drug administration to time of trial completion.

End point type	Secondary
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End point timeframe:

0 to 14 days after surgery

End point values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53 <sup>[3]</sup>	25	29	
Units: hours				
median (confidence interval 95%)	12.4 (1.2 to 999)	1.2 (0.7 to 1.5)	1.4 (1.0 to 4.1)	

Notes:

[3] - input: 999 = not available

## Statistical analyses

Statistical analysis title	Statistical Analysis for Time to First Opioid Re
Comparison groups	SABER-Bupivacaine v SABER-Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.014
Method	Logrank

Notes:

[4] - Exploratory comparison between SABER-Bupivacaine and Bupivacaine HCl was not analyzed inferentially.

## Secondary: Opioid Related Side Effects

End point title	Opioid Related Side Effects
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End point description:

Opioid-related side effects were recorded 0 to 7 days after surgery. The Opioid-Related Symptom Distress Scale (OR-SDS) is a composite score computed from a questionnaire containing frequent opioid-related symptoms (Fatigue, Drowsiness, Inability to concentrate, Nausea, Dizziness, Constipation, Itching, Difficulty with urination, Confusion, Retching/vomiting). For each symptom, participants assigned integer scores to assess severity (none=0 to very severe=4), bothersomeness (none=0 to very much=5), and frequency (none=0 to almost constantly=4); participants reported number of

Retching/vomiting episodes (none=0, 1-2 episodes=1, 3-4 episodes=2, 5-6 episodes=3, >6 episodes=4).

On each day (Days 0 to 7), the score for each symptom was the mean of the three component scores, and the OR-SDS score was the overall mean of the 10 symptom scores, (values from 0 to 4; larger outcomes are worse). The mean of the daily OR-SDS score from Days 0 to 7 gave the overall OR-SDS Score.

End point type	Secondary
End point timeframe:	
0 to 7 days after surgery	

End point values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	21	23	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.22 (± 0.35)	0.22 (± 0.24)	0.25 (± 0.24)	

## Statistical analyses

<b>Statistical analysis title</b>	Opioid Related Side Effects
Comparison groups	SABER-Bupivacaine v SABER-Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
P-value	= 0.773
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.14
Variability estimate	Standard deviation
Dispersion value	0.08

Notes:

[5] - Exploratory comparison between SABER-Bupivacaine and Bupivacaine HCl not analyzed inferentially

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

0 to 7 days after surgery

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	SABER-Bupivacaine
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Reporting group description:

5 mL, single dose instilled subacromially

Reporting group title	SABER-placebo
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Reporting group description:

5 mL, single dose instilled subacromially

Reporting group title	Bupivacaine HCl
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Reporting group description:

0.25% 20 mL, single dose instilled subacromially

Serious adverse events	SABER-Bupivacaine	SABER-placebo	Bupivacaine HCl
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 53 (1.89%)	1 / 25 (4.00%)	4 / 29 (13.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Tongue paralysis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug intolerance			

subjects affected / exposed	0 / 53 (0.00%)	1 / 25 (4.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Respiratory, thoracic and mediastinal disorders</b>			
Pleurisy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 53 (1.89%)	0 / 25 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Musculoskeletal and connective tissue disorders</b>			
Musculoskeletal pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

<b>Non-serious adverse events</b>	SABER-Bupivacaine	SABER-placebo	Bupivacaine HCl
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 53 (20.75%)	10 / 25 (40.00%)	8 / 29 (27.59%)
<b>Investigations</b>			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)	2 / 25 (8.00%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Electrocardiogram T wave inversion			
subjects affected / exposed	2 / 53 (3.77%)	0 / 25 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Blood pressure increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 25 (0.00%) 0	1 / 29 (3.45%) 1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 53 (3.77%)	1 / 25 (4.00%)	1 / 29 (3.45%)
occurrences (all)	3	1	1
Eye contusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 25 (4.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Incision site vesicles			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	1 / 25 (4.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 25 (4.00%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 25 (4.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 25 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 53 (5.66%)	1 / 25 (4.00%)	1 / 29 (3.45%)
occurrences (all)	4	2	1
Hypoaesthesia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 25 (4.00%)	1 / 29 (3.45%)
occurrences (all)	2	1	1

Dizziness subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 25 (4.00%) 1	1 / 29 (3.45%) 1
Migraine subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 25 (0.00%) 0	1 / 29 (3.45%) 1
General disorders and administration site conditions Discomfort subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 25 (4.00%) 1	0 / 29 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	3 / 25 (12.00%) 3	1 / 29 (3.45%) 1
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 25 (4.00%) 1	0 / 29 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)  Pharyngeal haematoma subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0  0 / 53 (0.00%) 0	0 / 25 (0.00%) 0  1 / 25 (4.00%) 1	1 / 29 (3.45%) 1  0 / 29 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus generalised subjects affected / exposed occurrences (all)  Erythema subjects affected / exposed occurrences (all)  Hidradenitis subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2  0 / 53 (0.00%) 0  0 / 53 (0.00%) 0	0 / 25 (0.00%) 0  0 / 25 (0.00%) 0  1 / 25 (4.00%) 1	0 / 29 (0.00%) 0  1 / 29 (3.45%) 1  0 / 29 (0.00%) 0





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2008	This amendment was made to change all text pertaining to the use of 15 mg morphine tablets as rescue therapy. Due to the unavailability of the 15 mg dose in some of the participating countries, 10 mg tablets were used to ensure that all countries were adhering to the same rescue medication regimen. Additionally, this amendment clarified the timings for the evaluation of home readiness via Post-Anaesthetic Discharge Scoring System.
23 January 2009	<p>In addition to the correction of some administrative errors, this amendment detailed, added, or clarified: the addition of the long-term safety visit, that the participant's evaluability would be decided at the Blinded Data Review Meeting, the allowance of intravenous morphine administration post-operatively to optimise the participant's pain treatment, the recording of background treatment (in the electronic case report form, not the electronic Diary [eDiary]), flexibility regarding the taking of PK blood samples, the use of alternative anaesthesia during surgery, the causality statement for adverse events, the definition of "at rest", the recording of concomitant illness (not past illness) and additional information regarding the safety of benzyl alcohol was added. Additionally, exclusion criterion number 16 was added to the protocol in this amendment. The schedule of assessments was updated in accordance with the changes.</p> <p>Twenty-three (23) participants were randomised at the time of this amendment.</p>
13 July 2009	<p>In addition to a clarification of some text, this amendment detailed that paracetamol should only be taken on Days 0 to 2 (72 hours) instead of Days 0 to 7. The paracetamol background treatment was not limited to orally administered paracetamol and was administered immediately after surgery to ensure that there was sufficient pain relief from background medication and subsequent adherence to the protocol. The amendment also detailed the removal of the baseline blood-draw as it was identical to the screening blood-draw and that alternative syringes were packed with the Investigational Medicinal Product (IMP) to avoid application of the incorrect volume of IMP following surgery. Additionally, anti-emetic use was clarified.</p> <p>Ninety -three (93) participants were randomised at the time of this amendment.</p>
11 December 2009	<p>The number of sites planned was updated to 20. The procedures for the collection of PK samples were clarified, which included decreasing the number of participants having blood samples taken for PK being reduced and clarifying that for participants not selected for PK profiling, a blood sample for PK analysis should be taken in case of any cardiac or central nervous system events.</p> <p>One hundred seven (107) participants were randomised at the time of this amendment.</p>

25 February 2010	<p>The wording of the amended protocol concerning paracetamol (that is, stopping use of paracetamol after 3 days [Amendment 3]) unintentionally resulted in not allowing for other analgesics other than rescue morphine from Days 3 to 7. The issue of as a high number of participants had mild pain, manageable with a weak analgesic. It was not considered acceptable in the light of standard practice and the World Health Organization analgesics ladder to allow only morphine during this part of the trial. Therefore the use of paracetamol was reinstated on an as-needed basis for the period from 72 hours to 7 days post-surgery. Morphine could still be used by those participants requiring a stronger analgesic or rescue medication. A file note from the Sponsor, Nycomed (03 March 2010) also clarified this decision. Clarification of the use of ondansetron as antiemetic treatment, even though listed in the Appendix 1 of the protocol, was included.</p> <p>During routine monitoring visits, a number of discrepancies in the recording of oral morphine rescue medication in the eDiary, as compared to the medication dispensed, were identified through discussions with the site personnel and the source data verification process.</p> <p>Due to an inconsistency in the process for resolving queries on eDiary data, one eDiary entry for a participant was overlooked when cleaning the data in accordance with the procedure described above. As a consequence an additional analysis of the total morphine equivalent dosage was performed with morphine equivalent dosage for this participant set to 0. There was 1 change to the planned analysis. The pair-wise comparison of placebo versus standard bupivacaine HCl for opioid consumption was excluded.</p> <p>One hundred twenty-six (126) participants were randomised at the time of this amendment.</p>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported