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 Undergoing Primary, Elective, Open, Abdominal Hysterectomy

Summary

EudraCT number	2007-006121-26
Trial protocol	DE GB HU FR SE LV
Global end of trial date	01 June 2010

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-001-IM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00993226
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	DURECT Corporation
Sponsor organisation address	10260 Bubb Road, Cupertino, CA, United States, 95014
Public contact	Deborah Scott, DURECT Corporation, 001 408-777-1417, deborah.scott@durect.com
Scientific contact	Deborah Scott, DURECT Corporation, 001 408-777-1417, deborah.scott@durect.com

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 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2010
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 instilled SABER-Bupivacaine for postoperative pain control in abdominal hysterectomy for a non-malignant indication on the basis of efficacy, safety, and pharmacokinetics (PK) evaluations.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guideline, 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	26 May 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	Sweden: 7
Country: Number of subjects enrolled	Hungary: 79
Country: Number of subjects enrolled	Latvia: 29
Worldwide total number of subjects	115
EEA total number of subjects	115

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)	114

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened 1 to 14 days before abdominal hysterectomy 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
Arm title	SABER-Bupivacaine

Arm description:

5 mL, single dose instilled into surgical incision

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:

SABER-Bupivacaine 5.0 millilitre (mL) (600 [milligram] mg bupivacaine) was administered as a single instillation into the surgical wound following hysterectomy. Following the closure of the fascia, a 16G (large bore) needle was used to draw up the correct volume of room temperature SABER-Bupivacaine into a syringe. The needle was then removed and the investigational product was administered; after the closure of the fascia a single dose of 5.0 mL of SABER-Bupivacaine was instilled (no needle) covering the whole fascia area and ensuring containment of the entire dose.

Arm title	SABER-Placebo

Arm description:

5 mL, single dose instilled into surgical incision

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

Dosage and administration details:

SABER-Placebo 5.0 mL was administered as a single instillation into the surgical wound following hysterectomy. Following the closure of the fascia, a 16G (large bore) needle was used to draw up the correct volume of room temperature SABER-Placebo into a syringe. The needle was then removed and the placebo was administered; after the closure of the fascia a single dose of 5.0 mL of SABER-Placebo was instilled (no needle) covering the whole fascia area and ensuring containment of the entire dose.

Arm title	Bupivacaine HCl

Arm description:

0.25% 40 mL, single dose infiltrated peri-incisionally

Arm type	Active comparator
Investigational medicinal product name	Bupivacaine HCl
Investigational medicinal product code	
Other name	Marcain
Pharmaceutical forms	Solution for injection
Routes of administration	Infiltration

Dosage and administration details:

The participant received 40 mL of standard bupivacaine HCl (Marcain; 100 mg bupivacaine HCl) following surgery, before wound closure, via infiltration: 10 mL was injected into the proximal muscle layer; 10 mL was injected into the distal layer, and 20 mL was injected into the subcutaneous layer.

Number of subjects in period 1	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Started	61	27	27
Completed	60	26	27
Not completed	1	1	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	SABER-Bupivacaine
Reporting group description:	
5 mL, single dose instilled into surgical incision	
Reporting group title	SABER-Placebo
Reporting group description:	
5 mL, single dose instilled into surgical incision	
Reporting group title	Bupivacaine HCl
Reporting group description:	
0.25% 40 mL, single dose infiltrated peri-incisionally	

Reporting group values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Number of subjects	61	27	27
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)	60	27	27
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.7	44.3	45.1
full range (min-max)	29 to 66	37 to 53	35 to 55
Gender categorical Units: Subjects			
Female	61	27	27
Male	0	0	0
BMI Units: kg/m^2			
arithmetic mean	26.1	26.2	27
full range (min-max)	19 to 33.2	19.4 to 34.1	18.3 to 35

Reporting group values	Total		
Number of subjects	115		
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)	114		
From 65-84 years	1		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	115		
Male	0		
BMI			
Units: kg/m^2			
arithmetic mean			
full range (min-max)	-		

End points

End points reporting groups	
Reporting group title	SABER-Bupivacaine
Reporting group description:	
5 mL, single dose instilled into surgical incision	
Reporting group title	SABER-Placebo
Reporting group description:	
5 mL, single dose instilled into surgical incision	
Reporting group title	Bupivacaine HCl
Reporting group description:	
0.25% 40 mL, single dose infiltrated peri-incisionally	

Primary: Pain Intensity (PI)	
End point title	Pain Intensity (PI)
End point description:	
Mean PI on movement area under concentration-time curve (AUC) over the period 1 to 72 hours post-surgery. Participants assessed their pain intensity using an 11-point PI Numeric Rating Scale (PI-NRS) with NRS scores ranging from 0 (no pain) to 10 (worst pain possible). 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:	
1 to 72 hours after surgery	

End point values	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	27	27	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Pain Intensity (PI)	4.15 (± 1.74)	4.46 (± 1.48)	4.27 (± 1.69)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Pain Intensity (PI)
Comparison groups	SABER-Bupivacaine v SABER-Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.467
Method	t-test in analysis of variance (ANOVA)
Parameter estimate	Least-square (LS) Mean Difference
Point estimate	-0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.36
Variability estimate	Standard deviation
Dispersion value	0.29

Notes:

[1] - Exploratory comparison between SABER-Bupivacaine and Bupivacaine HCl 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	61	27	27	
Units: mg				
arithmetic mean (standard deviation)	22.8 (± 24.3)	26.3 (± 25.7)	23.9 (± 25.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Supplemental Opioid Use
Comparison groups	SABER-Bupivacaine v SABER-Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.331
Method	t-test in ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.59
upper limit	2.58
Variability estimate	Standard deviation
Dispersion value	2.57

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

End point description:

End point type	Secondary

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	61	27	27	
Units: hour				
arithmetic mean (standard deviation)	7.71 (± 45.79)	1.53 (± 1.56)	25.94 (± 87.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Opioid Related Side Effects

End point title	Opioid Related Side Effects

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 to 2 episodes=1, 3 to 4 episodes=2, 5 to 6 episodes=3, >6 episodes=4).

On each day (Days 0 to 7), the score for each symptom was the mean of the 3 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	53	25	23	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.28 (± 0.28)	0.34 (± 0.31)	0.27 (± 0.24)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0 to 7 days after surgery	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	SABER-Bupivacaine
Reporting group description: -	
Reporting group title	SABER-Placebo
Reporting group description: -	
Reporting group title	Bupivacaine HCl
Reporting group description: -	

Serious adverse events	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 60 (11.67%)	0 / 27 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
ECG QT prolonged			
subjects affected / exposed	1 / 60 (1.67%)	0 / 27 (0.00%)	0 / 27 (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
ECG abnormal			
subjects affected / exposed	2 / 60 (3.33%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal neoplasm			
subjects affected / exposed	1 / 60 (1.67%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	1 / 60 (1.67%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Haematoma infection			
subjects affected / exposed	2 / 60 (3.33%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SABER-Bupivacaine	SABER-Placebo	Bupivacaine HCl
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 60 (81.67%)	24 / 27 (88.89%)	24 / 27 (88.89%)
Investigations			
Blood potassium decreased			
subjects affected / exposed	4 / 60 (6.67%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences (all)	4	1	0
C-reactive protein increased			
subjects affected / exposed	7 / 60 (11.67%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences (all)	7	0	1
White blood cell count increased			
subjects affected / exposed	1 / 60 (1.67%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Incision site haematoma			
subjects affected / exposed	3 / 60 (5.00%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Post procedural contusion			

subjects affected / exposed	36 / 60 (60.00%)	9 / 27 (33.33%)	0 / 27 (0.00%)
occurrences (all)	37	9	0
Post procedural discharge			
subjects affected / exposed	1 / 60 (1.67%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 60 (6.67%)	1 / 27 (3.70%)	2 / 27 (7.41%)
occurrences (all)	4	1	2
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 27 (3.70%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 60 (15.00%)	3 / 27 (11.11%)	4 / 27 (14.81%)
occurrences (all)	9	3	4
Somnolence			
subjects affected / exposed	5 / 60 (8.33%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	5	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 60 (16.67%)	4 / 27 (14.81%)	3 / 27 (11.11%)
occurrences (all)	10	4	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 60 (11.67%)	3 / 27 (11.11%)	7 / 27 (25.93%)
occurrences (all)	8	3	7
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 60 (15.00%)	8 / 27 (29.63%)	4 / 27 (14.81%)
occurrences (all)	9	8	5
Nausea			
subjects affected / exposed	8 / 60 (13.33%)	6 / 27 (22.22%)	9 / 27 (33.33%)
occurrences (all)	9	6	9
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 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.
20 January 2009	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.
25 March 2009	This amendment introduced the magnetic resonance imaging scan at the 6 month follow-up visit and the benzyl alcohol concentration measurements and analysis at selected sites. Eighty-one (81) participants were randomised according to the protocol version 5.0 including amendments 1 to 3.
13 July 2009	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. Thirty-four (34) participants were randomised according to protocol version 5.0 including amendments 1 to 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported