



## Clinical trial results:

### ED95 doses of commonly used local anaesthetic agents for ultrasound guided brachial plexus blocks

#### Summary

EudraCT number	2010-018466-22
Trial protocol	GB
Global end of trial date	14 May 2018

#### Results information

Result version number	v1 (current)
This version publication date	20 July 2019
First version publication date	20 July 2019

#### Trial information

##### Trial identification

Sponsor protocol code	AN09/9220
-----------------------	-----------

##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Woodhouse lane, Leeds, United Kingdom,
Public contact	Dr Anurag Vats, University of Leeds, anuragvats@nhs.net
Scientific contact	Dr Anurag Vats, University of Leeds, anuragvats@nhs.net

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	30 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2018
Global end of trial reached?	Yes
Global end of trial date	14 May 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To find out the doses (of the most commonly used local anaesthetic agents) that have 95% chance of success for ultrasound guided brachial plexus blocks in patients scheduled for upper limb surgery.

(Ultrasound guided brachial plexus block refers to injection of the local anaesthetic drug around the nerves supplying sensation to the shoulder and the arm under ultrasound guidance)

Protection of trial subjects:

The study was conducted according to the Good Clinical Practice (GCP) guidelines, and was regularly audited/monitored by the sponsor. All investigators connected to the study were GCP trained. All patients provided a written informed consent after considering the research information, and discussion with a GCP trained investigator. The study was approved by the local research ethics committee including amendments. We made provisions for securing safeguards of confidentiality of research data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	146

From 65 to 84 years	51
85 years and over	3

## Subject disposition

### Recruitment

Recruitment details:

Inclusion criteria: ASA 1-3 patients, Age >18 years, Patients of both sexes, Patients undergoing upper limb and shoulder surgery

Exclusion criteria: ASA > 3, Age <18 years, Allergy to local anaesthetic agent, Unable to give written informed consent, Body Mass Index >40, Pregnant woman. All patient were recruited at a single site in the trial period

### Pre-assignment

Screening details:

Patients were provided patient information sheet in the pre-assessment clinic, acute care admission ward for arm, forearm and hand injuries and/or by post as soon as they were listed for an upper limb surgery on a theatre list managed by the designated operator. (As agreed with the local ethics committee. )

### Pre-assignment period milestones

Number of subjects started	200
Number of subjects completed	200

### Period 1

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

Blinding implementation details:

The patient, the investigator performing the nerve block (the operator) and the investigator assessing it (the assessor) were blinded to the IMP type and dose. The dose of respective IMP was divided equally in multiple syringes which were covered completely with an opaque tape to blind the investigator. The assessor was not present at the time of administration of local anaesthetic. This method of blinding has been used in our institute in previous studies and has proven to be successful.

### Arms

Are arms mutually exclusive?	Yes
Arm title	Levo-bupivacaine 0.25% for interscalene brachial plexus block.

Arm description:

The patients recruited in this arm of the study were listed for a shoulder surgery and had an interscalene brachial plexus block sited under a general anaesthetic as per the protocol. The interscalene arm of the study is a dose-finding trial for 0.25% levo-bupivacaine and is not randomised. Efficacy of the block was assessed by VAPS pain scores at 15, 30, 60 and 120 minute intervals after the patient comes to recovery (PACU), where 0 mm on a 100 mm scale is no pain and 100 mm is the worst imaginable pain.

Arm type	Experimental
Investigational medicinal product name	Levo-bupivacaine 0.25%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Perineural use

Dosage and administration details:

The brachial plexus block was performed once the patient was in the anaesthetic room by the designated investigator (operator) using direct ultrasound guidance, under a general anaesthetic as per the protocol. The interscalene part of the brachial plexus was visualised using a Sonosite S Nerve ultrasound machine. The nerve block needle was passed under ultrasound guidance so that its tip lies adjacent to the brachial plexus. After negative aspiration from the needle the study dose of 0.25% levo-

bupivacaine was injected. This was done under ultrasound visualisation to ensure correct location of the needle is maintained and the spread of drug is uniform. The first dose used was 30 ml of levo-bupivacaine 0.25%, which is closest to the ED95. Subsequent doses were based on continual reassessment method as per the guidance of statistical support team with maximum ceiling of 50 ml. We have used the supply of IMP available in our hospital provided by a MA holding company in the country.

<b>Arm title</b>	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s
------------------	---

**Arm description:**

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to either receive prilocaine 1% or lidocaine 1% with adrenaline (1:200,000) for an ultrasound guided supraclavicular block. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Arm type	Experimental
Investigational medicinal product name	Lidocaine 1% with adrenaline (Epinephrine) 1:200,000 and Prilocaine 1 %
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Perineural use

**Dosage and administration details:**

The brachial plexus block was performed once in the anaesthetic room by a designated investigator under direct ultrasound guidance and standard monitoring . The overlying skin was infiltrated with 1% Lidocaine and a nerve block needle passed under ultrasound guidance so that its tip lies adjacent to the brachial plexus. After negative aspiration from the needle the study dose of lidocaine 1% with adrenaline (1:200,000) or prilocaine 1% was injected as per the randomisation. This was done under direct ultrasound visualisation to ensure correct location of the needle is maintained. The starting dose in each group (lidocaine 1% with adrenaline or prilocaine 1%) was 30mls, which is the closest to the estimated ED95. Subsequent doses were based on continual reassessment method as per the guidance of statistical support team with maximum ceiling of 40 ml for each IMP. We have used the supply of IMP available in our hospital provided by a MA holding company in the country.

<b>Arm title</b>	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
------------------	---

**Arm description:**

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to receive either lidocaine 1% with adrenaline (1:200,000) or lidocaine 2% with adrenaline (1:200,000) for an ultrasound guided axillary block under a local anaesthetic skin infiltration. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Arm type	Experimental
Investigational medicinal product name	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Perineural use

**Dosage and administration details:**

The brachial plexus block was performed once in the anaesthetic room by a designated investigator under standard monitoring. The four terminal branches of brachial plexus were visualized using an ultrasound machine. The overlying skin was infiltrated with 1% Lidocaine and a nerve block needle was passed under ultrasound guidance so that its tip lies adjacent to the branches of the brachial plexus. After negative aspiration from the needle the study dose of lidocaine 1% or lidocaine 2% [each with adrenaline (1:200,000)] was injected as per the randomisation. This was done under direct ultrasound visualisation to ensure correct location of the needle is maintained. The first dose used was 15 ml for the lidocaine 2% with adr group and 30 ml for the lidocaine 1% with adr group, which is closest to the estimated ED95. Subsequent doses were based on continual reassessment method as per the guidance of statistical support team. We used the standard supply of IMP available in our hospital.

<b>Number of subjects in period 1</b>	Levo-bupivacaine 0.25% for interscalene brachial plexus block.	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
Started	46	73	81
Completed	46	73	81

## Baseline characteristics

### Reporting groups

Reporting group title	Levo-bupivacaine 0.25% for interscalene brachial plexus block.
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for a shoulder surgery and had an interscalene brachial plexus block sited under a general anaesthetic as per the protocol. The interscalene arm of the study is a dose-finding trial for 0.25% levo-bupivacaine and is not randomised. Efficacy of the block was assessed by VAPS pain scores at 15, 30, 60 and 120 minute intervals after the patient comes to recovery (PACU), where 0 mm on a 100 mm scale is no pain and 100 mm is the worst imaginable pain.

Reporting group title	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to either receive prilocaine 1% or lidocaine 1% with adrenaline (1:200,000) for an ultrasound guided supraclavicular block. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Reporting group title	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to receive either lidocaine 1% with adrenaline (1:200,000) or lidocaine 2% with adrenaline (1:200,000) for an ultrasound guided axillary block under a local anaesthetic skin infiltration. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Reporting group values	Levo-bupivacaine 0.25% for interscalene brachial plexus block.	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
Number of subjects	46	73	81
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Subject population for all three arms were ASA grade I to III, both male and female, attending for upper limb surgery. We recorded patient's date of birth for age calculations.			
Units: years			
median	54.5	60	42
inter-quartile range (Q1-Q3)	40.25 to 65	50 to 69	25 to 59

Gender categorical			
Units: Subjects			
Female	16	44	26
Male	30	29	55

<b>Reporting group values</b>	Total		
Number of subjects	200		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Subject population for all three arms were ASA grade I to III, both male and female, attending for upper limb surgery. We recorded patient's date of birth for age calculations.			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	86		
Male	114		



## End points

### End points reporting groups

Reporting group title	Levo-bupivacaine 0.25% for interscalene brachial plexus block.
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for a shoulder surgery and had an interscalene brachial plexus block sited under a general anaesthetic as per the protocol. The interscalene arm of the study is a dose-finding trial for 0.25% levo-bupivacaine and is not randomised. Efficacy of the block was assessed by VAPS pain scores at 15, 30, 60 and 120 minute intervals after the patient comes to recovery (PACU), where 0 mm on a 100 mm scale is no pain and 100 mm is the worst imaginable pain.

Reporting group title	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for S
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to either receive prilocaine 1% or lidocaine 1% with adrenaline (1:200,000) for an ultrasound guided supraclavicular block. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Reporting group title	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
-----------------------	--

#### Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to receive either lidocaine 1% with adrenaline (1:200,000) or lidocaine 2% with adrenaline (1:200,000) for an ultrasound guided axillary block under a local anaesthetic skin infiltration. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

### Primary: Success of a block

End point title	Success of a block
-----------------	--------------------

#### End point description:

##### Successful block:

Supraclavicular and Axillary approaches: Absence of sensation to cold and pin prick at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb, 30 min after the block.

Interscalene approach: VAPS (scale from 0-100) in the operated shoulder of < 10 mm, at 120 minutes after admission to the post-anaesthesia care unit (PACU).

End point type	Primary
----------------	---------

#### End point timeframe:

For supraclavicular and axillary block: 10 minutes, 20 minutes and 30 minutes after the injection of a local anaesthetic ; For interscalene block: 15 minutes, 30 minutes, 60 minutes and 120 minutes after a patient arrives in the recovery room

<b>End point values</b>	Levo-bupivacaine 0.25% for interscalene brachial plexus block.	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	70 <sup>[1]</sup>	80 <sup>[2]</sup>	
Units: numbers				
Successful block	41	52	66	
Failed block	5	19	14	
Technical failure	0	3	1	

Notes:

[1] - As per the protocol

[2] - as per the protocol

## Statistical analyses

<b>Statistical analysis title</b>	ED95 estimates using the CRM (interscalene)
-----------------------------------	---

Statistical analysis description:

We set explicit inclusion and exclusion criteria, study stopping criteria and had clearly defined end points for patients recruited in the trial. The initial sample size of 40 patients to get reliable estimates of the ED95 dose was estimated after a sensitivity analysis. The modified CRM is a sequential dose allocation method based on the Bayesian analysis that uses aggregated published data, doses and responses of previous studies as well as the present allocated doses to advise further doses

Comparison groups	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s v Levo-bupivacaine 0.25% for interscalene brachial plexus block.
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0 <sup>[4]</sup>
Method	CRM
Parameter estimate	adaptive
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	99
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[3] - The ED95 dose estimate was determined using the modified CRM method (one parameter model). The posterior response probability of each dose level was re-estimated after inclusion of each cohort (2 patients). The dose allocated to each new cohort of patients was the dose level with the updated posterior response probability closest to 0.95. The dose-finding allocation was performed using R software version 3.2.2 (R cran). The study was stopped when the best estimate of ED95 was achieved.

[4] - Not applicable

<b>Statistical analysis title</b>	ED95 estimates using the CRM ( supraclavicular)
-----------------------------------	---

Statistical analysis description:

We set explicit inclusion/exclusion criteria, study stopping criteria and had clearly defined end points for patients recruited in the trial. The total sample size of 40 patients/arm to get reliable estimates of the ED95 dose was estimated after a sensitivity analysis. The modified CRM is a sequential dose allocation method based on the Bayesian analysis that uses aggregated published data, doses and responses of previous studies as well as the present allocated doses to advise further doses.

Comparison groups	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for
-------------------	--

	s v Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	= 0 <sup>[6]</sup>
Method	CRM
Parameter estimate	adaptive
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	99
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[5] - The ED95 dose was determined using the modified CRM method (one parameter model). The posterior response probability of each dose level was re-estimated after inclusion of each cohort (2 patients). The dose allocated to each new cohort of patients was the dose level with the updated posterior response probability closest to 0.95. The dose-finding allocation was performed using R software version 3.2.2 (R cran). The study was stopped when study stopping criteria were met for respective study arms.

[6] - not applicable

<b>Statistical analysis title</b>	ED95 estimates using the CRM (Axillary)
-----------------------------------	---

Statistical analysis description:

We set explicit inclusion/exclusion criteria, study stopping criteria and had clearly defined end points for patients recruited in the trial. The initial sample size of 40 patients/arm to get reliable estimates of the ED95 dose was estimated after a sensitivity analysis. The modified CRM is a sequential dose allocation method based on the Bayesian analysis that uses aggregated published data, doses and responses of previous studies as well as the present allocated doses to advise further doses.

Comparison groups	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f v Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	= 0 <sup>[8]</sup>
Method	CRM
Parameter estimate	adaptive
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	99
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[7] - The ED95 dose estimate was determined using the modified CRM method (one parameter model). The posterior response probability of each dose level was re-estimated after inclusion of each cohort (2 patients). The dose allocated to each new cohort of patients was the dose level with the updated posterior response probability closest to 0.95. The dose-finding allocation was performed using R software version 3.2.2 (R cran). The study was stopped when the best estimate of ED95 was achieved.

[8] - not applicable

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events occurring up to 24 hours following administration or before discharge from hospital (whichever is earlier) will be reported

Adverse event reporting additional description:

Adverse events will be identified either by the Chief Investigator (CI) in the peri-operative period, the Principal Investigator (PI) during the following 24 hours or before the discharge by the nursing staff on the post-operative wards. The PI will report adverse event data as per the protocol.

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	SNOMED CT
-----------------	-----------

Dictionary version	1.36.4
--------------------	--------

### Reporting groups

Reporting group title	Levo-bupivacaine 0.25% for interscalene brachial plexus block.
-----------------------	--

Reporting group description:

The patients recruited in this arm of the study were listed for a shoulder surgery and had an interscalene brachial plexus block sited under a general anaesthetic as per the protocol. The interscalene arm of the study is a dose-finding trial for 0.25% levo-bupivacaine and is not randomised. Efficacy of the block was assessed by VAPS pain scores at 15, 30, 60 and 120 minute intervals after the patient comes to recovery (PACU), where 0 mm on a 100 mm scale is no pain and 100 mm is the worst imaginable pain.

Reporting group title	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s
-----------------------	--

Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to either receive prilocaine 1% or lidocaine 1% with adrenaline (1:200,000) for an ultrasound guided supraclavicular block. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Reporting group title	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
-----------------------	--

Reporting group description:

The patients recruited in this arm of the study were listed for an elbow, forearm or hand surgery. Consenting and eligible patients were randomised to receive either lidocaine 1% with adrenaline (1:200,000) or lidocaine 2% with adrenaline (1:200,000) for an ultrasound guided axillary block under a local anaesthetic skin infiltration. Efficacy of the block was assessed at 10-minute intervals after siting the block, for up to 30 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold (i.e. at 10, 20, 30, minutes after the injection is finished).

Serious adverse events	Levo-bupivacaine 0.25% for interscalene brachial plexus block.	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	0 / 73 (0.00%)	0 / 81 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

<b>Non-serious adverse events</b>	Levo-bupivacaine 0.25% for interscalene brachial plexus block.	Lidocaine 1% with adrenaline 1:200,000 and Prilocaine 1% for s	Lidocaine 1% and lidocaine 2% each with adrenaline 1:200,000 f
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	1 / 73 (1.37%)	0 / 81 (0.00%)
Gastrointestinal disorders			
Nausea, Vomiting	Additional description: Postoperative		
subjects affected / exposed	1 / 46 (2.17%)	1 / 73 (1.37%)	0 / 81 (0.00%)
occurrences (all)	1	1	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2012	Research ethics committee approval for increasing the number of trial subject to up to 300 patients
14 August 2017	Research ethics committee approval for modifying the way we provide patient information sheet to potential participants

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 August 2017	Patient recruitment halted while the amendment was being considered by the research ethics committee.	19 September 2017

Notes:

### Limitations and caveats

None reported