



## Clinical trial results:

**Clinical trial of the investigational medicinal product, local anaesthetic levo-bupivacaine in infants 3 - 6 months post natal age.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-000393-34 |
| Trial protocol           | GB             |
| Global end of trial date | 06 June 2017   |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 November 2019 |
| First version publication date | 07 November 2019 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | R03003 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | -               |
| WHO universal trial number (UTN)   | -               |
| Other trial identifiers            | REC: 15/NW/0240 |

Notes:

### Sponsors

|                              |                                                                                                           |
|------------------------------|-----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Manchester University NHS Foundation Trust                                                                |
| Sponsor organisation address | Cobbet House, Manchester, United Kingdom, M13 9WU                                                         |
| Public contact               | Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 1612764125, lynne.webster@cmft.nhs.uk  |
| Scientific contact           | Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 161 2764125, lynne.webster@cmft.nhs.uk |

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:

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**Results analysis stage**

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|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 06 June 2017 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 06 June 2017 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 06 June 2017 |
| Was the trial ended prematurely?                     | No           |

Notes:

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**General information about the trial**

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Main objective of the trial:

The main objective is to ratify the safety of the present standard protocol for caudal-epidural levobupivacaine in infants three to six months age.

A bolus of levo-bupivacaine will be used, followed by an infusion in the same space, after one hour of the bolus. This study will measure plasma levels of levo-bupivacaine upto 72 hours, though the infusion will stop at 48 hours, to ensure that toxic levels are not reached in plasma.

It will help to confirm the pharmacokinetic model and the information will also be used to manage other infants undergoing other major surgery and requiring this method of pain relief.

Protection of trial subjects:

At present, infants undergoing repair of a Bladder Exstrophy have a caudal-epidural where appropriate, to provide pain relief. The local anaesthetic Levo-bupivacaine is infused through a catheter. Previous researchers have found it difficult to obtain repeated blood samples in this age group over long periods of 48 - 72 hours.

Our study population of infants with Bladder Exstrophy, all require invasive monitoring intra-operatively which is left in situ post-operatively. Blood samples can therefore be obtained without discomfort to the infants or additional injections and bruising.

WHO recommendations for safe limits of blood sampling will be adhered to for this research.

Assay of levo-bupivacaine requires specialised equipment and this will be done in Clinical Pathology laboratory at Nottingham. The blood sample obtained in our hospital will be centrifuged and only the plasma will be transported by designated couriers at appropriate temperatures.

Each study participant will be allocated a unique study number at recruitment and all data will be linked to this number for transport.

Identifiable patient data will be collected by one investigator and stored in paper and electronic form in the trust

Background therapy:

All patients will receive Clonidine as per current hospital guidelines except those infants under 5 kg. 1.5 ug/ml will be added to the bag.

Evidence for comparator:

There is no comparator in this study as it is a single arm study.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 15 June 2015 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects   | 8                 |
| EEA total number of subjects         | 8                 |

Notes:

| <b>Subjects enrolled per age group</b>    |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 8 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 0 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from Royal Manchester Children's Hospital, part of Manchester University NHS Foundation Trust. Opened to recruitment 12/06/2015 and lasted 24 months.

### Pre-assignment

Screening details:

Only those infants whose patients consent to a caudal-epidural block, as well as to this study will be included. Preoperative assessment will be carried out one week prior to surgery by the PI who will discuss the anaesthetic process and provide an information sheet. Consent will be taken on the morning of the operation.

### Period 1

|                              |                           |
|------------------------------|---------------------------|
| Period 1 title               | Baseline (overall period) |
| Is this the baseline period? | Yes                       |
| Allocation method            | Not applicable            |
| Blinding used                | Not blinded               |

Blinding implementation details:

Single arm study

### Arms

|           |                  |
|-----------|------------------|
| Arm title | Levo-bupivacaine |
|-----------|------------------|

Arm description:

Single arm study. Infusion of Levo-bupivacaine 0.2 mg/kg/hr, by the caudal - epidural route, started one hour after a bolus dose of 2 mg/kg.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Levo-bupivacaine                |
| Investigational medicinal product code | PL 41042/0005                   |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Epidural use                    |

Dosage and administration details:

2.0 mg/kg given as a bolus over 5 minutes. Infusion of 0.2 mg/kg/hr will start at 60 minutes after the completion of the bolus and will run for 48 hours. Clonidine will be added to this caudal-epidural infusion bag. This is a single administration during surgery.

|                                       |                  |
|---------------------------------------|------------------|
| <b>Number of subjects in period 1</b> | Levo-bupivacaine |
| Started                               | 8                |
| Completed                             | 8                |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description: -

| Reporting group values                             | Baseline | Total |  |
|----------------------------------------------------|----------|-------|--|
| Number of subjects                                 | 8        | 8     |  |
| Age categorical                                    |          |       |  |
| Units: Subjects                                    |          |       |  |
| In utero                                           | 0        | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0        | 0     |  |
| Newborns (0-27 days)                               | 0        | 0     |  |
| Infants and toddlers (28 days-23 months)           | 8        | 8     |  |
| Children (2-11 years)                              | 0        | 0     |  |
| Adolescents (12-17 years)                          | 0        | 0     |  |
| Adults (18-64 years)                               | 0        | 0     |  |
| From 65-84 years                                   | 0        | 0     |  |
| 85 years and over                                  | 0        | 0     |  |
| Age continuous                                     |          |       |  |
| Units: months                                      |          |       |  |
| arithmetic mean                                    | 5.0      |       |  |
| standard deviation                                 | ± 0.5    | -     |  |
| Gender categorical                                 |          |       |  |
| Units: Subjects                                    |          |       |  |
| Female                                             | 3        | 3     |  |
| Male                                               | 5        | 5     |  |
| Body weight                                        |          |       |  |
| Units: kg                                          |          |       |  |
| arithmetic mean                                    | 6.90     |       |  |
| standard deviation                                 | ± 0.96   | -     |  |

## End points

### End points reporting groups

|                                                                                                                                                                              |                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                        | Levo-bupivacaine |
| Reporting group description:<br>Single arm study. Infusion of Levo-bupivacaine 0.2 mg/kg/hr, by the caudal - epidural route, started one hour after a bolus dose of 2 mg/kg. |                  |

### Primary: Total levobupivacaine serum concentration

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Total levobupivacaine serum concentration <sup>[1]</sup> |
|-----------------|----------------------------------------------------------|

End point description:

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

End point timeframe:

1 hour

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

| End point values              | Levo-bupivacaine    |  |  |  |
|-------------------------------|---------------------|--|--|--|
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 8                   |  |  |  |
| Units: mg/L                   |                     |  |  |  |
| median (full range (min-max)) | 0.30 (0.20 to 0.70) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Total levobupivacaine concentration

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | Total levobupivacaine concentration <sup>[2]</sup> |
|-----------------|----------------------------------------------------|

End point description:

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

End point timeframe:

47 hours

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                               |                     |  |  |  |
|-------------------------------|---------------------|--|--|--|
| <b>End point values</b>       | Levo-bupivacaine    |  |  |  |
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 7                   |  |  |  |
| Units: mg/L                   |                     |  |  |  |
| median (full range (min-max)) | 1.21 (0.07 to 1.85) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Levobupivacaine: Average apparent unbound clearance

|                          |                                                                    |
|--------------------------|--------------------------------------------------------------------|
| End point title          | Levobupivacaine: Average apparent unbound clearance <sup>[3]</sup> |
| End point description:   |                                                                    |
| Final parameter estimate |                                                                    |
| End point type           | Primary                                                            |
| End point timeframe:     |                                                                    |
| 1 hour to 72 hours       |                                                                    |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Levo-bupivacaine    |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 8                   |  |  |  |
| Units: L/h                       |                     |  |  |  |
| number (confidence interval 95%) | 61.3 (48.1 to 68.0) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Levobupivacaine: Apparent unbound volume of distribution

|                          |                                                                         |
|--------------------------|-------------------------------------------------------------------------|
| End point title          | Levobupivacaine: Apparent unbound volume of distribution <sup>[4]</sup> |
| End point description:   |                                                                         |
| Final parameter estimate |                                                                         |
| End point type           | Primary                                                                 |
| End point timeframe:     |                                                                         |
| 1 hour to 72 hours       |                                                                         |

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

| End point values                 | Levo-bupivacaine    |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 8                   |  |  |  |
| Units: L/h                       |                     |  |  |  |
| number (confidence interval 95%) | 1.05 (0.62 to 1.27) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: AAG conversion clearance

|                          |                                         |
|--------------------------|-----------------------------------------|
| End point title          | AAG conversion clearance <sup>[5]</sup> |
| End point description:   |                                         |
| Final parameter estimate |                                         |
| End point type           | Primary                                 |
| End point timeframe:     |                                         |
| 1 hour to 72 hours       |                                         |

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

| End point values                 | Levo-bupivacaine       |  |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 8                      |  |  |  |
| Units: L/h                       |                        |  |  |  |
| number (confidence interval 95%) | 0.136 (0.125 to 0.141) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: AAG: concentration of AAG and pre-AAG at time zero

|                          |                                                                   |
|--------------------------|-------------------------------------------------------------------|
| End point title          | AAG: concentration of AAG and pre-AAG at time zero <sup>[6]</sup> |
| End point description:   |                                                                   |
| Final parameter estimate |                                                                   |



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

End point timeframe:

Time 0

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                                  |                  |  |  |  |
|----------------------------------|------------------|--|--|--|
| <b>End point values</b>          | Levo-bupivacaine |  |  |  |
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 8                |  |  |  |
| Units: mg/L                      |                  |  |  |  |
| number (confidence interval 95%) | 413 (292 to 475) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: AAG: Interaction term

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | AAG: Interaction term <sup>[7]</sup> |
|-----------------|--------------------------------------|

End point description:

Final parameter estimates

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

End point timeframe:

1 hour to 72 hours

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Levo-bupivacaine    |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 8                   |  |  |  |
| Units: scale                     |                     |  |  |  |
| number (confidence interval 95%) | 4.58 (3.50 to 5.13) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: AAG: Proportion residual variability

|                          |                                                     |
|--------------------------|-----------------------------------------------------|
| End point title          | AAG: Proportion residual variability <sup>[8]</sup> |
| End point description:   |                                                     |
| Final parameter estimate |                                                     |
| End point type           | Primary                                             |
| End point timeframe:     |                                                     |
| 1 hour to 72 hours       |                                                     |

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                                  |                      |  |  |  |
|----------------------------------|----------------------|--|--|--|
| <b>End point values</b>          | Levo-bupivacaine     |  |  |  |
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 8                    |  |  |  |
| Units: Percentage                |                      |  |  |  |
| number (confidence interval 95%) | 7.81 (4.25 to 14.34) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Levobupivacaine: first-order absorption rate

|                           |                                                             |
|---------------------------|-------------------------------------------------------------|
| End point title           | Levobupivacaine: first-order absorption rate <sup>[9]</sup> |
| End point description:    |                                                             |
| Final parameter estimates |                                                             |
| End point type            | Primary                                                     |
| End point timeframe:      |                                                             |
| 1 hour to 72 hours        |                                                             |

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | Levo-bupivacaine      |  |  |  |
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 8                     |  |  |  |
| Units: L/h                       |                       |  |  |  |
| number (confidence interval 95%) | 0.15 (0.138 to 0.156) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Primary: Levobupivacaine: Proportional residual variability**

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|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Levobupivacaine: Proportional residual variability <sup>[10]</sup> |
|-----------------|--------------------------------------------------------------------|

End point description:

Final parameter estimates

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

End point timeframe:

1 hour to 72 hours

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was primarily a pharmacokinetic study, looking at total serum levobupivacaine concentrations after a caudalepidural loading dose followed by a maintenance infusion over 48 hours in infants aged 36 months. The outcome measures describe the concentrations, but in this study there are no hypotheses to test. The main outcomes are from a pharmacokinetic model.

| End point values                 | Levo-<br>bupivacaine |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 8                    |  |  |  |
| Units: Percentage                |                      |  |  |  |
| number (confidence interval 95%) | 33 (12.15 to 89.72)  |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Adverse events will be collected for the time the patient is in the study.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |   |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Whole cohort |
|-----------------------|--------------|

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: As this study is only small, using a drug which is already protocol, there were no non-serious adverse events noted.

| Serious adverse events                            | Whole cohort                                                                  |  |  |
|---------------------------------------------------|-------------------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                                                               |  |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)                                                                |  |  |
| number of deaths (all causes)                     | 0                                                                             |  |  |
| number of deaths resulting from adverse events    | 0                                                                             |  |  |
| Respiratory, thoracic and mediastinal disorders   |                                                                               |  |  |
| Tachypnoea                                        | Additional description: Additional symptoms included Tachycardia and Rhinitis |  |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)                                                                |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                         |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                         |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Whole cohort  |  |  |
|-------------------------------------------------------|---------------|--|--|
| Total subjects affected by non-serious adverse events |               |  |  |
| subjects affected / exposed                           | 0 / 8 (0.00%) |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment                                                                                                                                                                                                                                         |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 May 2015 | Change to the trial protocol as requested by the MHRA following their initial review of the clinical trial application. The changes related to additional exclusion criteria and additional rationale for drug dosing for the bolus and infusion. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported