



## Clinical trial results:

**Prospective, double-blind, randomised trial to assess the efficacy of continuous sciatic/posterior tibial nerve blockade via a neural sheath catheter in lower limb amputees**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2007-000619-27 |
| Trial protocol           | GB             |
| Global end of trial date | 30 April 2013  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 27 December 2019 |
| First version publication date | 27 December 2019 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 56481676 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN68691928 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University Hospitals of Leicester NHS Trust   |
| Sponsor organisation address | Research & Innovation, Trust HQ. Level 3 Balmoral Building. Leicester Royal Infirmary. , Leicester, United Kingdom, LE1 5WW |
| Public contact               | Carolyn Maloney, University Hospitals of Leicester NHS Trust, +44 116 258 4109, carolyn.maloney@uhl-tr.nhs.uk               |
| Scientific contact           | Prof. Jonathan Thompson, University Hospitals of Leicester NHS Trust, jt23@le.ac.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                       | 30 April 2013 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 April 2013 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 2013 |
| 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:

To establish the effects of continuous peri- and post-operative sciatic/posterior tibial nerve blockade using a levobupivacaine infusion via a neural sheath catheter on late stump pain, phantom limb sensations and phantom limb pain.

Protection of trial subjects:

All trial subjects (including intervention and control groups) received patient-controlled analgesia with morphine. All patients had access to further escape medication according to the protocol as required

Background therapy:

Standardised surgery performed under standardised general anaesthesia

Evidence for comparator:

Pain scores, requirements for analgesia, quality of life questionnaires

|   |                     |
|---|---------------------|
| Actual start date of recruitment                          | 01 October 2007     |
| Long term follow-up planned                               | Yes                 |
| Long term follow-up rationale                             | Scientific research |
| Long term follow-up duration                              | 12 Months           |
| Independent data monitoring committee (IDMC) involvement? | Yes                 |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 90 |
| Worldwide total number of subjects   | 90                 |
| EEA total number of subjects         | 90                 |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 27 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 48 |
| 85 years and over   | 15 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment October 2007 to March 2013. Single UK centre

### Pre-assignment

Screening details:

All patients admitted to the vascular unit at Leicester Royal Infirmary and planned for major lower limb amputation surgery (due to vascular aetiology) were considered for inclusion

### Period 1

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

Blinding implementation details:

Computer generated randomisation by an independent clinical trials unit

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Intervention group |

Arm description:

infusion of 0.125% Levobupivacaine at a rate of 8mls h<sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | levobupivacaine 0.125% |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Infusion               |
| Routes of administration               | Perineural use         |

Dosage and administration details:

infusion of 0.125% Levobupivacaine at a rate of 8mls h<sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | placebo control arm |
|------------------|---------------------|

Arm description:

infusion of 0.9% saline at a rate of 8mls h<sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively.

|  |                |
|--|----------------|
| Arm type                               | Placebo        |
| Investigational medicinal product name | 0.9% saline    |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Infusion       |
| Routes of administration               | Perineural use |

Dosage and administration details:

infusion of 0.9% saline at a rate of 8mls h<sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively.

| <b>Number of subjects in period 1</b> | Intervention group | placebo control arm |
|---------------------------------------|--------------------|---------------------|
| Started                               | 45                 | 45                  |
| Completed                             | 41                 | 40                  |
| Not completed                         | 4                  | 5                   |
| Adverse event, serious fatal          | -                  | 1                   |
| Consent withdrawn by subject          | 1                  | -                   |
| Protocol deviation                    | 3                  | 4                   |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Recruitment |
|-----------------------|-------------|

Reporting group description: -

| Reporting group values                             | Recruitment | Total |  |
|--|-------------|-------|--|
| Number of subjects                                 | 90          | 90    |  |
| 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)           | 0           | 0     |  |
| Children (2-11 years)                              | 0           | 0     |  |
| Adolescents (12-17 years)                          | 0           | 0     |  |
| Adults (18-64 years)                               | 27          | 27    |  |
| From 65-84 years                                   | 48          | 48    |  |
| 85 years and over                                  | 15          | 15    |  |
| 18 -100  | 0           | 0     |  |
| Adults aged 18-64                                  | 0           | 0     |  |
| Age continuous                                     |             |       |  |
| Female   |             |       |  |
| Units: years                                       |             |       |  |
| median   | 72          |       |  |
| inter-quartile range (Q1-Q3)                       | 62 to 82    | -     |  |
| Gender categorical                                 |             |       |  |
| Male   |             |       |  |
| Units: Subjects                                    |             |       |  |
| Female   | 32          | 32    |  |
| Male   | 58          | 58    |  |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Intervention group  |
| Reporting group description:<br>infusion of 0.125% Levobupivacaine at a rate of 8mls h <sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively. |                     |
| Reporting group title   | placebo control arm |
| Reporting group description:<br>infusion of 0.9% saline at a rate of 8mls h <sup>-1</sup> for 96hrs via a neural sheath catheter into the sciatic or posterior tibial nerve for above and below knee amputations respectively.            |                     |

### Primary: Presence or absence of significant phantom limb pain

|   |  |
|---|--|
| End point title                                     | Presence or absence of significant phantom limb pain |
| End point description:                              |  |
| End point type                                      | Primary  |
| End point timeframe:<br>6 months after intervention |  |

| End point values            | Intervention group | placebo control arm |  |  |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type          | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed | 30                 | 32                  |  |  |
| Units: number               | 7                  | 8                   |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | chi squared test                         |
| Comparison groups                       | Intervention group v placebo control arm |
| Number of subjects included in analysis | 62                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other                                    |
| P-value                                 | < 0.05                                   |
| Method                                  | Chi-squared                              |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

6 months

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

### Dictionary used

|                 |     |
|-----------------|-----|
| Dictionary name | OED |
|-----------------|-----|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | experimental |
|-----------------------|--------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | experimental     | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed   | 22 / 41 (53.66%) | 24 / 43 (55.81%) |  |
| number of deaths (all causes)                                       | 7                | 6                |  |
| number of deaths resulting from adverse events                      | 7                | 6                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Lung cancer metastatic  |                  |                  |  |
| subjects affected / exposed   | 1 / 41 (2.44%)   | 0 / 43 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 1            | 0 / 0            |  |
| Brain Tumour  |                  |                  |  |
| subjects affected / exposed   | 1 / 41 (2.44%)   | 0 / 43 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Vascular disorders  |                  |                  |  |
| Deep vein thrombosis postoperative                                  |                  |                  |  |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 1 / 43 (2.33%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Lower limb ischemia   |                  |                  |  |



|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 3 / 41 (7.32%)   | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2  | 0 / 1           |  |
| Ischaemic small bowel                           |  |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           |  |
| femoral and iliac vein thrombosis               |  |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| CVA   |  |                 |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1           |  |
| Saddle embolus                                  |  |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| mesenteric vascular occlusion                   |  |                 |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Surgical and medical procedures                 |  |                 |  |
| Revision of amputation                          | Additional description: Below knee to above knee amputations |                 |  |
| subjects affected / exposed                     | 7 / 41 (17.07%)  | 5 / 43 (11.63%) |  |
| occurrences causally related to treatment / all | 0 / 7  | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| loop colostomy                                  |  |                 |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| SMA Embolectomy                                 |  |                 |  |

|   |  |                |  |
|---|--|----------------|--|
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Amputation  | Additional description: Vascular insufficiency left AKA                    |                |  |
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| left CFA endarterectomy and a left profundaplasty |  |                |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Angioplasty                                       |  |                |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Amputation of toes                                | Additional description: Debridement and amputation of 1st,2nd and 3rd toes |                |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| iliac and profunda thrombectomy                   |  |                |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| axillo femoral bypass.                            |  |                |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Right hemicolectomy                               |  |                |  |
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Reproductive system and breast disorders          |  |                |  |

|   |  |                |  |
|---|--|----------------|--|
| Recto vaginal fistula                           |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |  |                |  |
| Exacerbation COPD                               |  |                |  |
| subjects affected / exposed                     | 2 / 41 (4.88%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Pulmonary oedema                                |  |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Pneumonia                                       |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1          |  |
| pulmonary embolism                              |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| pulmonary nodules                               | Additional description: possible lung metastasis |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Chest Infection                                 |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Psychiatric disorders                           |  |                |  |
| Dementia  |  |                |  |
| subjects affected / exposed                     | 2 / 41 (4.88%)                                   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 2  | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| disassociation disorder                         |                |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| delirium  |                |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Confusional state                               |                |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 4 / 43 (9.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychosis postoperative                         |                |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Depression                                      |                |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Fall  |                |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Myocardial infarction                           |                |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Cardiac arrest                                  |                |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |

|   |  |                |  |
|---|--|----------------|--|
| SVT   |  |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| ECG changes                                     |  |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| IHD   |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0          |  |
| Gastrointestinal disorders                      |  |                |  |
| PR Bleeding                                     |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Vomiting  | Additional description: admitted with 24hr history of vomiting |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| small bowel ischaemia                           |  |                |  |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0          |  |
| Haematemesis due to severe eosophagitis         |  |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Hepatobiliary disorders                         |  |                |  |
| Hepatic encephalopathy                          |  |                |  |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 43 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1          |  |

|  |  |                |  |
|--|--|----------------|--|
| Elevated Liver function tests<br>subjects affected / exposed | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Skin and subcutaneous tissue disorders                       |  |                |  |
| Cellulitis   |  |                |  |
| subjects affected / exposed                                  | 1 / 41 (2.44%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Erythema   | Additional description: right leg                |                |  |
| subjects affected / exposed                                  | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Ulcer  | Additional description: Non healing leg Ulcer    |                |  |
| subjects affected / exposed                                  | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| peri orbital swelling  |  |                |  |
| subjects affected / exposed                                  | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Stage 3 pressure sore  |  |                |  |
| subjects affected / exposed                                  | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 1          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Endocrine disorders  |  |                |  |
| Hypoglycaemia  |  |                |  |
| subjects affected / exposed                                  | 0 / 41 (0.00%)                                   | 1 / 43 (2.33%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0  | 0 / 0          |  |
| deaths causally related to<br>treatment / all                | 0 / 0  | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders              |  |                |  |
| Hairline pelvic fracture                                     | Additional description: Fall leading to fracture |                |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Bakers Cyst                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Amputation wound infection                      |                |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 6 / 43 (13.95%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infected Axillo femoral graft                   |                |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Venous ulceration infection                     |                |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infected axillo femoral graft                   |                |                 |  |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 43 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pressure sore infection                         |                |                 |  |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 43 (2.33%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | experimental    | Placebo        |  |
|---|-----------------|----------------|--|
| Total subjects affected by non-serious adverse events |                 |                |  |
| subjects affected / exposed                           | 6 / 41 (14.63%) | 4 / 43 (9.30%) |  |
| Gastrointestinal disorders                            |                 |                |  |
| nausea and vomiting                                   |                 |                |  |
| subjects affected / exposed                           | 6 / 41 (14.63%) | 4 / 43 (9.30%) |  |
| occurrences (all)                                     | 1               | 1              |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported