



## Clinical trial results:

### A Phase IIa trial of 177 Lutetium Dotatate in Children with Primary Refractory or Relapsed High-Risk Neuroblastoma

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-000510-10   |
| Trial protocol           | GB               |
| Global end of trial date | 16 February 2018 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 07 October 2018 |
| First version publication date | 07 October 2018 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RG_11-141 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN98918118 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Birmingham  |
| Sponsor organisation address | Edgbaston, Birmingham, Birmingham, United Kingdom, B15 2TT                            |
| Public contact               | Emmanouela Gbandi, University of Birmingham, 0044 01214143799, ludo@trials.bham.ac.uk |
| Scientific contact           | Emmanouela Gbandi, University of Birmingham, 0044 01214143799, ludo@trials.bham.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**

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 17 September 2018 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 16 February 2018  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 16 February 2018  |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

Main objective of the trial:

The trial will evaluate how effective <sup>177</sup>Lutetium DOTATATE is in children with high-risk relapsed or refractory neuroblastoma and determine the safety and adverse events of the treatment experienced by patients on the study.

Protection of trial subjects:

Not applicable

Background therapy:

None mandated in the protocol

Evidence for comparator:

Not applicable

|   |                               |
|---|-------------------------------|
| Actual start date of recruitment                          | 19 September 2013             |
| Long term follow-up planned                               | Yes                           |
| Long term follow-up rationale                             | Scientific research, Efficacy |
| Long term follow-up duration                              | 5 Years                       |
| Independent data monitoring committee (IDMC) involvement? | Yes                           |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 21 |
| Worldwide total number of subjects   | 21                 |
| EEA total number of subjects         | 21                 |

Notes:

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**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)  | 1  |
| Children (2-11 years)                     | 19 |
| Adolescents (12-17 years)                 | 1  |
| Adults (18-64 years)                      | 0  |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

One site was activated in the UK in March 2013 and first patient was recruited on 19 September 2013. The last patient was recruited on 28 July 2017. The trial was closed to recruitment on 16 February 2018. 21 patients in total were recruited.

### Pre-assignment

Screening details:

No screening assessments involved. Please refer to the protocol for the eligibility criteria.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall trial baseline (overall period) |
| Is this the baseline period? | Yes                                     |
| Allocation method            | Non-randomised - controlled             |
| Blinding used                | Not blinded                             |

Blinding implementation details:

Not applicable

### Arms

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | LuDO Treatment |
|------------------|----------------|

Arm description:

177 Lutetium DOTATATE

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | 177 Lutetium DOTATATE                 |
| Investigational medicinal product code | Not applicable                        |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

The first administered activity of 177Lutetium DOTATATE = 75MBq/kg . The administered activity for the subsequent administrations will depend on the whole body dose received and the haematological toxicity from the previous administration (detailed instructions included in the trial protocol)

| <b>Number of subjects in period 1</b> | LuDO Treatment |
|---------------------------------------|----------------|
| Started                               | 21             |
| Completed                             | 8              |
| Not completed                         | 13             |
| Progression and Death                 | 1              |
| Adverse event, non-fatal              | 1              |
| Death                                 | 1              |
| Progression                           | 10             |

## Baseline characteristics

### Reporting groups

|  |                        |
|--|------------------------|
| Reporting group title  | Overall trial baseline |
| Reporting group description:   |                        |
| This group contains the full number of patients that took part in stage 1 of this phase IIa study. |                        |

| Reporting group values                                     | Overall trial baseline | Total |  |
|--|------------------------|-------|--|
| Number of subjects   | 21                     | 21    |  |
| Age categorical  |                        |       |  |
| Units: Subjects  |                        |       |  |
| Infants and toddlers (28 days-23 months)                   | 1                      | 1     |  |
| Children (2-11 years)                                      | 19                     | 19    |  |
| Adolescents (12-17 years)                                  | 1                      | 1     |  |
| Age continuous   |                        |       |  |
| Units: years   |                        |       |  |
| median   | 5.4                    |       |  |
| inter-quartile range (Q1-Q3)                               | 4.4 to 8.0             | -     |  |
| Gender categorical   |                        |       |  |
| Units: Subjects  |                        |       |  |
| Female   | 11                     | 11    |  |
| Male   | 10                     | 10    |  |
| MYCN status at diagnosis                                   |                        |       |  |
| Units: Subjects  |                        |       |  |
| Amplified  | 1                      | 1     |  |
| Not amplified  | 20                     | 20    |  |
| INSS Stage at diagnosis                                    |                        |       |  |
| Units: Subjects  |                        |       |  |
| Stage 3  | 3                      | 3     |  |
| Stage 4  | 18                     | 18    |  |
| Number of relapses prior to registration in the LuDO trial |                        |       |  |
| Units: Subjects  |                        |       |  |
| Zero relapses  | 6                      | 6     |  |
| One relapse  | 11                     | 11    |  |
| Two relapses   | 1                      | 1     |  |
| Three relapses   | 1                      | 1     |  |
| Four relapses  | 2                      | 2     |  |
| Disease type   |                        |       |  |
| Units: Subjects  |                        |       |  |
| Not responsive   | 2                      | 2     |  |
| Persistent   | 3                      | 3     |  |
| Progressive  | 1                      | 1     |  |
| Progressive; Persistent; Not responsive                    | 2                      | 2     |  |
| Relapsed   | 11                     | 11    |  |
| Relapsed; Progressive                                      | 1                      | 1     |  |
| Relapsed; Progressive; Persistent; Not responsive          | 1                      | 1     |  |



## End points

### End points reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title                                 | LuDO Treatment              |
| Reporting group description:<br>177 Lutetium DOTATATE |                             |
| Subject analysis set title                            | Primary endpoint population |
| Subject analysis set type                             | Full analysis               |

Subject analysis set description:

The analysis of the primary outcome measure was carried out on an eligible and evaluable patient basis, i.e. patients who were ineligible and for whom primary outcome data was unavailable were excluded from the analysis (note: any patients who progressed or died prior to their 1 month end of treatment (EOT)

assessment were treated as non responders). Patients who did not start treatment and those who died due to any cause within 3 months from registration (i.e. time between death date and registration date is less than 92 days) were excluded from this analysis.

### Primary: Response at 1 month after EOT measured by INRC

|                 |  |
|-----------------|--|
| End point title | Response at 1 month after EOT measured by INRC |
|-----------------|--|

End point description:

- Response at 1 month after EOT measured by INRC. Complete, very good partial and partial response were count as responses for the purpose of the primary outcome.
- EOT was defined as the last administration of 177Lutetium DOTATATE.

Note: if there is no response assessment at 1 or 4 months post last administered course of 177Lutetium DOTATATE, the patient would be considered a non-responder.

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

End point timeframe:

Measured at 1 month after end of treatment (EOT).

| End point values            | LuDO Treatment  | Primary endpoint population |  |  |
|-----------------------------|-----------------|-----------------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set        |  |  |
| Number of subjects analysed | 21              | 14                          |  |  |
| Units: Response             |                 |                             |  |  |
| Responder                   | 0               | 0                           |  |  |
| Non responder               | 21              | 14                          |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Proportion of responders at 1 month by INRC |
|----------------------------|---|

Statistical analysis description:

Proportion of responders at 1 month by INRC with confidence intervals for eligible and evaluable patient population

|                   |  |
|-------------------|--|
| Comparison groups | LuDO Treatment v Primary endpoint population |
|-------------------|--|

|   |                                      |
|---|--------------------------------------|
| Number of subjects included in analysis | 35                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[1]</sup>                 |
| Parameter estimate                      | Proportion - analysis on 14 patients |
| Point estimate                          | 0                                    |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 1-sided                              |
| lower limit                             | 0                                    |

Notes:

[1] - Proportion of responders at 1 month with confidence intervals. Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed separately on two patient groups of 21 and 14 patients respectively.

## Secondary: Progression Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

Progression-free Survival is defined as the time from registration until objective tumour progression or death or to date of censoring for patients who do not experience the event during trial follow up.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Patients were followed up from registration until progression or death or last assessment date from patients who did not experience an event.

| End point values            | LuDO Treatment  | Primary endpoint population |  |  |
|-----------------------------|-----------------|-----------------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set        |  |  |
| Number of subjects analysed | 21              | 14 <sup>[2]</sup>           |  |  |
| Units: Months               | 21              | 0                           |  |  |

Notes:

[2] - This group was not analysed for Progression Free Survival

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Median Progression-free Survival (PFS)       |
| Comparison groups                       | LuDO Treatment v Primary endpoint population |
| Number of subjects included in analysis | 35   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[3]</sup>                         |
| Parameter estimate                      | Median PFS - analysis on 21 patients         |
| Point estimate                          | 2.96   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | 1.71   |
| upper limit                             | 7.66   |

Notes:

[3] - Median Progression-free Survival (PFS). Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed on 21 patients (overall trial population patients).

## Secondary: Overall Survival

|  |                  |
|--|------------------|
| End point title  | Overall Survival |
| End point description:<br>Overall Survival is defined as the time from registration into the trial until date of death (death from any cause) or to date of censoring for patients who do not experience the event during trial follow-up. |                  |
| End point type   | Secondary        |
| End point timeframe:<br>Patients were followed up from registration until death or last assessment date from patients who did not experience an event.   |                  |

| End point values            | LuDO Treatment  | Primary endpoint population |  |  |
|-----------------------------|-----------------|-----------------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set        |  |  |
| Number of subjects analysed | 21              | 14 <sup>[4]</sup>           |  |  |
| Units: Months               | 21              | 0                           |  |  |

Notes:

[4] - This group was not analysed for Overall Survival

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Median Overall Survival                      |
| Comparison groups                       | LuDO Treatment v Primary endpoint population |
| Number of subjects included in analysis | 35   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[5]</sup>                         |
| Parameter estimate                      | Median OS - analysis on 21 patients          |
| Point estimate                          | 13.04  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | 2.99   |
| upper limit                             | 21.52  |

Notes:

[5] - Median Overall Survival (OS). Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed on 21 patients (overall trial population patients).

## Secondary: Response at 4 month after EOT measured by INRC

|  |  |
|--|--|
| End point title  | Response at 4 month after EOT measured by INRC |
| End point description:   |  |
| End point type   | Secondary                                      |
| End point timeframe:<br>Response by International Neuroblastoma Response Criteria at 4 months after completion of therapy. |  |

| End point values            | LuDO Treatment  | Primary endpoint population |  |  |
|-----------------------------|-----------------|-----------------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set        |  |  |
| Number of subjects analysed | 21              | 14 <sup>[6]</sup>           |  |  |
| Units: Response at 4 months |                 |                             |  |  |
| Responder                   | 0               | 0                           |  |  |
| Non responder               | 21              | 0                           |  |  |

Notes:

[6] - This group was not analysed for Response at 4 months post EoT

## Statistical analyses

| Statistical analysis title                                     | Proportion of responders at 4 months         |
|--|--|
| Statistical analysis description:                              |  |
| Proportion of responders at 4 months with confidence intervals |  |
| Comparison groups  | LuDO Treatment v Primary endpoint population |
| Number of subjects included in analysis                        | 35   |
| Analysis specification   | Pre-specified                                |
| Analysis type  | other <sup>[7]</sup>                         |
| Parameter estimate   | Proportion - analysis on 21 patients         |
| Point estimate   | 0  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided                                      |
| lower limit  | 0  |
| upper limit  | 0.155  |

Notes:

[7] - Proportion - Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed separately on 21 patients (overall trial population patients).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events should be reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description: -

| Serious adverse events                               | Safety population |  |  |
|--|-------------------|--|--|
| Total subjects affected by serious adverse events    |                   |  |  |
| subjects affected / exposed                          | 6 / 20 (30.00%)   |  |  |
| number of deaths (all causes)                        | 18                |  |  |
| number of deaths resulting from adverse events       | 0                 |  |  |
| Investigations                                       |                   |  |  |
| Neutrophil count decreased                           |                   |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)    |  |  |
| occurrences causally related to treatment / all      | 1 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Injury, poisoning and procedural complications       |                   |  |  |
| vascular access complication                         |                   |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)    |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Fever  |                   |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)    |  |  |
| occurrences causally related to treatment / all      | 0 / 2             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Blood and lymphatic system disorders                 |                   |  |  |
| Febrile neutropenia                                  |                   |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Gastrointestinal disorders</b>               |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Stomach pain                                    |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| Device related infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Wound infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Other, specify: vesicular rash                  |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | Safety population |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 16 / 20 (80.00%)  |  |  |
| <b>Investigations</b>                                 |                   |  |  |
| Alanine aminotransferase increased                    |                   |  |  |
| subjects affected / exposed                           | 2 / 20 (10.00%)   |  |  |
| occurrences (all)                                     | 2                 |  |  |

|  |   |  |  |
|--|---|--|--|
| Alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1                             |  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1                             |  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)   | 6 / 20 (30.00%)<br>11                           |  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)   | 7 / 20 (35.00%)<br>10                           |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)   | 7 / 20 (35.00%)<br>8                            |  |  |
| White blood cell decreased<br>subjects affected / exposed<br>occurrences (all)   | 6 / 20 (30.00%)<br>10                           |  |  |
| Injury, poisoning and procedural complications<br>Vascular access complication<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1                             |  |  |
| Blood and lymphatic system disorders<br>Anemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)              | 4 / 20 (20.00%)<br>6<br><br>1 / 20 (5.00%)<br>1 |  |  |
| General disorders and administration site conditions<br>Fever<br>subjects affected / exposed<br>occurrences (all)<br><br>General disorders and administration site conditions - Other, specify | 6 / 20 (30.00%)<br>7                            |  |  |

|                                 |                 |  |  |
|---------------------------------|-----------------|--|--|
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Malaise                         |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Pain                            |                 |  |  |
| subjects affected / exposed     | 2 / 20 (10.00%) |  |  |
| occurrences (all)               | 2               |  |  |
| Gastrointestinal disorders      |                 |  |  |
| Abdominal pain                  |                 |  |  |
| subjects affected / exposed     | 2 / 20 (10.00%) |  |  |
| occurrences (all)               | 3               |  |  |
| Constipation                    |                 |  |  |
| subjects affected / exposed     | 4 / 20 (20.00%) |  |  |
| occurrences (all)               | 4               |  |  |
| Diarrhea                        |                 |  |  |
| subjects affected / exposed     | 3 / 20 (15.00%) |  |  |
| occurrences (all)               | 3               |  |  |
| Enterocolitis                   |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Gastritis                       |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Gastroesophageal reflux disease |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Mucositis oral                  |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Nausea                          |                 |  |  |
| subjects affected / exposed     | 2 / 20 (10.00%) |  |  |
| occurrences (all)               | 2               |  |  |
| Stomach pain                    |                 |  |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)               | 1               |  |  |

|  |  |  |  |
|--|--|--|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 3 / 20 (15.00%)<br>3   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>3   |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Periorbital edema<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin and subcutaneous tissue disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1 |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>2   |  |  |
| Infections and infestations<br>Bronchial infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Device related infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Infections and infestations - Other, specify<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin infection   | 1 / 20 (5.00%)<br>1<br><br>2 / 20 (10.00%)<br>2<br><br>2 / 20 (10.00%)<br>2                          |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1 |  |  |
| Upper respiratory infection<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 20 (5.00%)<br>1 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 20 (5.00%)<br>1 |  |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 20 (5.00%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Hypoalbuminemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 13 October 2014 | Amendment of protocol to v 2.0 03-Sep-2014 and age adapted Patient Information Sheets v3.0 12-May-2014<br>Summary of changes: <ul style="list-style-type: none"><li>• Adaptation of time schedule of investigations and IMP handling instructions due to IMP supply changes</li><li>• Change in SAE reporting due to new contract with manufacturer</li><li>• Amendment of follow up investigations</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption                            | Restart date      |
|---------------|---|-------------------|
| 01 March 2016 | Temporary halt due to IMP supply issues | 08 September 2016 |

Notes:

### Limitations and caveats

None reported