



## Clinical trial results:

**A phase II randomized, placebo-controlled, double-blind, dose controlled trial in patients suffering from early, newly developing abdominal or pulmonary derived septic organ dysfunction to evaluate safety, pharmacokinetics, pharmacodynamics and to estimate efficacy of the new humanized monoclonal i.v. administered antibody IFX-1**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-001037-40   |
| Trial protocol           | DE               |
| Global end of trial date | 03 December 2015 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 28 June 2021 |
| First version publication date | 28 June 2021 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | IFX-1-P2.1 |
|-----------------------|------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | InflaRx GmbH  |
| Sponsor organisation address | Winzerlaer Str.2, Jena, Germany, 07745  |
| Public contact               | Trial Coordination, ZKS Leipzig - KKS, 49 3419716154, SCIENS@zks.uni-leipzig.de |
| Scientific contact           | Trial Coordination, ZKS Leipzig - KKS, 49 3419716154, SCIENS@zks.uni-leipzig.de |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

---

**Results analysis stage**

---

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 23 September 2016 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 03 December 2015  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 03 December 2015  |
| Was the trial ended prematurely?                     | No                |

Notes:

---

**General information about the trial**

---

Main objective of the trial:

The primary objective of this trial was to characterize the safety and tolerability of three dose regimens of IFX-1 and also to perform an assessment of the pharmacokinetics and pharmacodynamics of IFX-1.

Protection of trial subjects:

This study was carried out in accordance with the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) Good Clinical Practice guidelines, the Declaration of Helsinki (Version of 1996), and standard operating procedures for clinical research and development at InflaRx GmbH and the Clinical Research Organizations involved.

Before admitting a subject into this study the subject had to provide written consent to participate in the study. The investigator was responsible to obtain informed consent in accordance with local laws.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

---

**Population of trial subjects**

---

**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 72 |
| Worldwide total number of subjects   | 72          |
| EEA total number of subjects         | 72          |

Notes:

---

**Subjects enrolled per age group**

---

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 30 |
| From 65 to 84 years                       | 36 |

|                   |   |
|-------------------|---|
| 85 years and over | 6 |
|-------------------|---|

## Subject disposition

### Recruitment

#### Recruitment details:

The study included male or female patients of 18 years or older with occurrence of at least 2 criteria of a systemic inflammatory response syndrome and a suspected or confirmed abdominal or pulmonary infection. Between 25 April 2014 and 3 December 2015, 72 subjects were screened in 17 centers in Germany.

### Pre-assignment

#### Screening details:

Of 2783 pre-screened patients, 72 patients were screened for eligibility before participating in the active treatment phase of the study. Subjects were not to be entered to the trial treatment if any of the eligibility criteria were violated. All of the 72 enrolled patients were randomized and treated.

### Period 1

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

#### Blinding implementation details:

All study participants were blinded with respect to IFX-1 and placebo. Standard measures were taken for the investigational medical product to ensure adequate blinding (e.g., same container/closure system, storage conditions, color, and foaming property).

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Placebo Combined |

#### Arm description:

Intravenous administration of placebo in any of the three cohorts corresponding to the Verum Cohorts 1, 2 and 3. The ratio between IFX-1 and placebo within one dose cohort was 2:1.

One patient completed the study at Day 28 after first treatment but stayed in hospital and had a serious fatal adverse event 4 weeks after study completion.

|  |                 |
|--|-----------------|
| Arm type                               | Placebo         |
| Investigational medicinal product name | Placebo         |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

#### Dosage and administration details:

The placebo is a phosphat buffered saline solution with polysorbate 80. Administration was following the same treatment schedule as IFX-1:

Cohort 1: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h

Cohort 2: 2 x 4 mg/kg b.w. on 0 h and 24 h

Cohort 3: 3 x 4 mg/kg b.w. on 0 h, 24 h, and 72 h

For patients weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Verum Cohort 1 |
|------------------|----------------|

#### Arm description:

Intravenous administration of IFX-1 according to the following schedule: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | IFX-1           |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

The amount of study drug for a single infusion was based on the body weight (b.w.) of the subject (mg/kg) and the treatment arm:

Cohort 1: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h

Cohort 2: 2 x 4 mg/kg b.w. on 0 h and 24 h

Cohort 3: 3 x 4 mg/kg b.w. on 0 h, 24 h, and 72 h

For patients weighing more than 100 kg the dose calculation was based on 100 kg b.w..

The volume of the administered IMP was calculated according to the following formula: Volume of IMP (in mL) = dose group (in mg/kg) x body weight (in kg) / 10 mg/mL. Afterwards the volume of IMP was filled up with sterile NaCl 0.9% solution used for injection to a total volume of 50 mL into a 50 mL infusion pump syringe. IFX-1 was supplied in 10 mL glass vials in strength of 10 mg/mL and is a monoclonal IgG4 anti-human C5a immunoglobulin.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Verum Cohort 2 |
|------------------|----------------|

**Arm description:**

Intravenous administration of IFX-1 according to the following schedule: 2 x 4 mg/kg body weight (b.w.) on 0 h and 24 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | IFX-1           |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

The amount of study drug for a single infusion was based on the body weight (b.w.) of the subject (mg/kg) and the treatment arm:

Cohort 1: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h

Cohort 2: 2 x 4 mg/kg b.w. on 0 h and 24 h

Cohort 3: 3 x 4 mg/kg b.w. on 0 h, 24 h, and 72 h

For patients weighing more than 100 kg the dose calculation was based on 100 kg b.w..

The volume of the administered IMP was calculated according to the following formula: Volume of IMP (in mL) = dose group (in mg/kg) x body weight (in kg) / 10 mg/mL. Afterwards the volume of IMP was filled up with sterile NaCl 0.9% solution used for injection to a total volume of 50 mL into a 50 mL infusion pump syringe. IFX-1 was supplied in 10 mL glass vials in strength of 10 mg/mL and is a monoclonal IgG4 anti-human C5a immunoglobulin.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Verum Cohort 3 |
|------------------|----------------|

**Arm description:**

Intravenous administration of IFX-1 according to the following schedule: 3 x 4 mg/kg body weight (b.w.) on 0 h, 24 h and 72 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | IFX-1           |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

The amount of study drug for a single infusion was based on the body weight (b.w.) of the subject (mg/kg) and the treatment arm:

Cohort 1: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h

Cohort 2: 2 x 4 mg/kg b.w. on 0 h and 24 h

Cohort 3: 3 x 4 mg/kg b.w. on 0 h, 24 h, and 72 h

For patients weighing more than 100 kg the dose calculation was based on 100 kg b.w..

The volume of the administered IMP was calculated according to the following formula: Volume of IMP (in mL) = dose group (in mg/kg) x body weight (in kg) / 10 mg/mL. Afterwards the volume of IMP was filled up with sterile NaCl 0.9% solution used for injection to a total volume of 50 mL into a 50 mL infusion pump syringe. IFX-1 was supplied in 10 mL glass vials in strength of 10 mg/mL and is a monoclonal IgG4 anti-human C5a immunoglobulin.

| <b>Number of subjects in period 1</b> | Placebo Combined | Verum Cohort 1 | Verum Cohort 2 |
|---------------------------------------|------------------|----------------|----------------|
| Started                               | 24               | 16             | 16             |
| Completed                             | 20               | 10             | 13             |
| Not completed                         | 4                | 6              | 3              |
| Adverse event, serious fatal          | 3                | 6              | 3              |
| Refusal of informed consent           | 1                | -              | -              |

| <b>Number of subjects in period 1</b> | Verum Cohort 3 |
|---------------------------------------|----------------|
| Started                               | 16             |
| Completed                             | 14             |
| Not completed                         | 2              |
| Adverse event, serious fatal          | 2              |
| Refusal of informed consent           | -              |

## Baseline characteristics

### Reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Placebo Combined |
| Reporting group description:<br>Intravenous administration of placebo in any of the three cohorts corresponding to the Verum Cohorts 1, 2 and 3. The ratio between IFX-1 and placebo within one dose cohort was 2:1.<br>One patient completed the study at Day 28 after first treatment but stayed in hospital and had a serious fatal adverse event 4 weeks after study completion. |                  |
| Reporting group title  | Verum Cohort 1   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |
| Reporting group title  | Verum Cohort 2   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 2 x 4 mg/kg body weight (b.w.) on 0 h and 24 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |
| Reporting group title  | Verum Cohort 3   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 3 x 4 mg/kg body weight (b.w.) on 0 h, 24 h and 72 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |

| Reporting group values                | Placebo Combined | Verum Cohort 1 | Verum Cohort 2 |
|---------------------------------------|------------------|----------------|----------------|
| Number of subjects                    | 24               | 16             | 16             |
| Age categorical<br>Units: Subjects    |                  |                |                |
| Adults (18-64 years)                  | 12               | 7              | 7              |
| From 65-84 years                      | 10               | 8              | 6              |
| 85 years and over                     | 2                | 1              | 3              |
| Gender categorical<br>Units: Subjects |                  |                |                |
| Female                                | 8                | 6              | 7              |
| Male                                  | 16               | 10             | 9              |

| Reporting group values                | Verum Cohort 3 | Total |  |
|---------------------------------------|----------------|-------|--|
| Number of subjects                    | 16             | 72    |  |
| Age categorical<br>Units: Subjects    |                |       |  |
| Adults (18-64 years)                  | 4              | 30    |  |
| From 65-84 years                      | 12             | 36    |  |
| 85 years and over                     | 0              | 6     |  |
| Gender categorical<br>Units: Subjects |                |       |  |
| Female                                | 5              | 26    |  |
| Male                                  | 11             | 46    |  |

## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Placebo Combined |
| Reporting group description:<br>Intravenous administration of placebo in any of the three cohorts corresponding to the Verum Cohorts 1, 2 and 3. The ratio between IFX-1 and placebo within one dose cohort was 2:1.<br>One patient completed the study at Day 28 after first treatment but stayed in hospital and had a serious fatal adverse event 4 weeks after study completion. |                  |
| Reporting group title  | Verum Cohort 1   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |
| Reporting group title  | Verum Cohort 2   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 2 x 4 mg/kg body weight (b.w.) on 0 h and 24 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |
| Reporting group title  | Verum Cohort 3   |
| Reporting group description:<br>Intravenous administration of IFX-1 according to the following schedule: 3 x 4 mg/kg body weight (b.w.) on 0 h, 24 h and 72 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.  |                  |

### Primary: IFX-1 plasma concentration

|   |  |
|---|--|
| End point title   | IFX-1 plasma concentration <sup>[1][2]</sup> |
| End point description:<br>Plasma concentration of IFX-1 at each time point.<br>Full Analysis Set (FAS): all subjects who were randomized and who received at least one dose of IFX-1.<br>Pharmacokinetic-Population (PK-PP): Only patients who were considered "meaningful evaluable" regarding their pharmacokinetics/pharmacodynamics laboratory measurements during the data review meeting are presented in this record. The number of subjects analysed varied between time points.<br><br>According to specifications made during the data review meeting, values below level of quantification were set to 0, if applicable.<br>For some time points, IFX-1 plasma concentration was not measured for all cohorts. Not applicable values are presented as "99999" or "-99999". |  |
| End point type  | Primary                                      |
| End point timeframe:<br>At 0 hours (h) and 2h, 6h, 12h, 14h (only verum cohort 1), 24h, 26h (only verum cohorts 2 and 3), 48h, 72h, 74h (only verum cohort 3), Day 5, Day 8, Day 13, Day 28 after first infusion of IFX-1 and at hospital discharge   |  |
| Notes:<br>[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.<br>Justification: Only descriptive analyses were defined and performed.<br>[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: IFX-1 plasma concentration was not presented for the Placebo Combined arm, as patients in this arm did not receive IFX-1 infusions.  |  |



| End point values                         | Verum Cohort 1            | Verum Cohort 2              | Verum Cohort 3             |  |
|--|---------------------------|-----------------------------|----------------------------|--|
| Subject group type                       | Reporting group           | Reporting group             | Reporting group            |  |
| Number of subjects analysed              | 13 <sup>[3]</sup>         | 12 <sup>[4]</sup>           | 13 <sup>[5]</sup>          |  |
| Units: µg/ml                             |                           |                             |                            |  |
| geometric mean (confidence interval 95%) |                           |                             |                            |  |
| 0 h                                      | 99999 (99999 to 99999)    | 99999 (99999 to 99999)      | 0.067 (-99999 to 99999)    |  |
| 2 h                                      | 33.215 (28.825 to 38.273) | 77.623 (64.689 to 93.142)   | 68.361 (58.776 to 79.508)  |  |
| 6 h                                      | 26.766 (22.964 to 31.198) | 61.634 (54.205 to 70.081)   | 60.067 (51.825 to 69.620)  |  |
| 12 h                                     | 19.351 (16.135 to 23.208) | 50.039 (42.114 to 59.457)   | 44.251 (37.898 to 51.668)  |  |
| 14 h                                     | 47.713 (40.187 to 56.648) | 99999 (99999 to 99999)      | 99999 (99999 to 99999)     |  |
| 24 h                                     | 33.347 (27.983 to 39.740) | 33.369 (27.375 to 40.675)   | 30.146 (25.014 to 36.332)  |  |
| 26 h                                     | 99999 (99999 to 99999)    | 102.133 (86.577 to 120.484) | 88.844 (77.471 to 101.887) |  |
| 48 h                                     | 16.035 (12.444 to 20.663) | 61.932 (52.028 to 73.721)   | 52.273 (41.223 to 66.285)  |  |
| 72 h                                     | 8.064 (5.366 to 12.117)   | 37.737 (30.285 to 47.023)   | 35.764 (26.823 to 47.685)  |  |
| 74 h                                     | 99999 (99999 to 99999)    | 99999 (99999 to 99999)      | 97.405 (85.671 to 110.748) |  |
| Day 5                                    | 2.848 (1.911 to 4.244)    | 16.131 (11.981 to 21.719)   | 41.906 (32.324 to 54.329)  |  |
| Day 8                                    | 0.715 (0.507 to 1.008)    | 3.951 (2.675 to 5.834)      | 14.051 (9.993 to 19.758)   |  |
| Day 13                                   | 0.191 (0.092 to 0.399)    | 1.080 (0.436 to 2.675)      | 3.069 (1.835 to 5.132)     |  |
| Day 28                                   | 99999 (99999 to 99999)    | 0.230 (0.118 to 0.450)      | 0.452 (0.298 to 0.686)     |  |
| Hospital discharge                       | 0.249 (0.033 to 1.889)    | 0.767 (0.129 to 4.548)      | 14.676 (-99999 to 99999)   |  |

Notes:

[3] - FAS, PK-PP

[4] - FAS, PK-PP

[5] - FAS, PK-PP

## Statistical analyses

No statistical analyses for this end point

## Primary: Cmax

End point title Cmax<sup>[6][7]</sup>

End point description:

Maximum observed IFX-1 plasma concentration (C<sub>max</sub>) by treatment (FAS, PK-PP).

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

End point timeframe:

At 0 hours (h) and 2h, 6h, 12h, 14h (only cohort 1), 24h, 26h (only cohorts 2 and 3), 48h, 72h, 74h (only cohort 3), Day 5, Day 8, Day 13, Day 28 after first infusion of IFX-1 and at hospital discharge

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: Only descriptive analyses were defined and performed.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: C<sub>max</sub> was not presented for the Placebo Combined arm, as patients in this arm did not receive IFX-1 infusions.

| End point values                         | Verum Cohort 1         | Verum Cohort 2           | Verum Cohort 3           |  |
|--|------------------------|--------------------------|--------------------------|--|
| Subject group type                       | Reporting group        | Reporting group          | Reporting group          |  |
| Number of subjects analysed              | 13 <sup>[8]</sup>      | 12 <sup>[9]</sup>        | 13 <sup>[10]</sup>       |  |
| Units: µg/mL                             |                        |                          |                          |  |
| geometric mean (confidence interval 95%) | 47.71 (40.19 to 56.65) | 103.25 (87.08 to 122.42) | 103.63 (92.22 to 116.46) |  |

Notes:

[8] - FAS, PK-PP

[9] - FAS, PK-PP

[10] - FAS, PK-PP

## Statistical analyses

No statistical analyses for this end point

## Primary: Cthrough

|                 |                              |
|-----------------|------------------------------|
| End point title | Cthrough <sup>[11][12]</sup> |
|-----------------|------------------------------|

End point description:

IFX-1 plasma concentration measured directly before infusion (Cthrough) by treatment and infusion (FAS, PK-PP). The number of subjects analysed varied between infusions.

Not applicable values are presented as "99999" or "-99999".

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

End point timeframe:

Directly before infusions: for Cohort 1 at 0h and 12h, for Cohort 2 at 0h and 24h, and for Cohort 3 at 0h, 14h and 72h.

Notes:

[11] - 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: Only descriptive analyses were defined and performed.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cthrough was not presented for the Placebo Combined arm, as patients in this arm did not receive IFX-1 infusions.

| End point values                         | Verum Cohort 1            | Verum Cohort 2            | Verum Cohort 3            |  |
|--|---------------------------|---------------------------|---------------------------|--|
| Subject group type                       | Reporting group           | Reporting group           | Reporting group           |  |
| Number of subjects analysed              | 13 <sup>[13]</sup>        | 12 <sup>[14]</sup>        | 13 <sup>[15]</sup>        |  |
| Units: µg/mL                             |                           |                           |                           |  |
| geometric mean (confidence interval 95%) |                           |                           |                           |  |
| First infusion                           | 99999 (99999 to 99999)    | 99999 (99999 to 99999)    | 0.067 (-99999 to 99999)   |  |
| Second infusion                          | 19.351 (16.135 to 23.208) | 33.369 (27.375 to 40.675) | 30.146 (25.014 to 36.332) |  |
| Third infusion                           | 99999 (99999 to 99999)    | 99999 (99999 to 99999)    | 35.764 (26.823 to 47.685) |  |

Notes:

[13] - FAS, PK-PP

[14] - FAS, PK-PP

[15] - FAS, PK-PP

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC

|   |                                     |
|---|-------------------------------------|
| End point title   | AUC <sup>[16]</sup> <sup>[17]</sup> |
| End point description:  |                                     |
| Area under the curve (AUC) of IFX-1 plasma concentration (FAS, PK-PP)   |                                     |
| End point type  | Primary                             |
| End point timeframe:  |                                     |
| At 0 hours (h) and 2h, 6h, 12h, 14h (only verum cohort 1), 24h, 26h (only verum cohorts 2 and 3), 48h, 72h, 74h (only verum cohort 3), Day 5, Day 8, Day 13, Day 28 after first infusion of IFX-1 and at hospital discharge |                                     |

Notes:

[16] - 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: Only descriptive analyses were defined and performed.

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: AUC for IFX-1 plasma concentration was not calculated for the Placebo Combined arm, as patients in this arm did not receive IFX-1 infusions.

| End point values                         | Verum Cohort 1            | Verum Cohort 2            | Verum Cohort 3              |  |
|--|---------------------------|---------------------------|-----------------------------|--|
| Subject group type                       | Reporting group           | Reporting group           | Reporting group             |  |
| Number of subjects analysed              | 13 <sup>[18]</sup>        | 12 <sup>[19]</sup>        | 13 <sup>[20]</sup>          |  |
| Units: h*µg/mL                           |                           |                           |                             |  |
| geometric mean (confidence interval 95%) | 2101.4 (1690.2 to 2612.7) | 6345.7 (5320.6 to 7568.2) | 10799.6 (9232.8 to 12632.3) |  |

Notes:

[18] - FAS, PK-PP

[19] - FAS, PK-PP

[20] - FAS, PK-PP

## Statistical analyses

No statistical analyses for this end point

### Primary: C5a concentration

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | C5a concentration <sup>[21]</sup> |
|-----------------|-----------------------------------|

End point description:

Plasma concentration of free, detectable C5a at each time point (FAS).

The number of subjects analysed varied between time points.

Not applicable values are presented as "99999" or "-99999".

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

End point timeframe:

At 0 hours (h) and 2h, 6h, 12h, 24h, 72h, Day 5, Day 8, Day 13, Day 28 after first infusion of IFX-1 or placebo and at hospital discharge

Notes:

[21] - 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: Performed statistical analyses were solely related to data exploration/description.

| End point values                         | Placebo Combined    | Verum Cohort 1      | Verum Cohort 2      | Verum Cohort 3         |
|--|---------------------|---------------------|---------------------|------------------------|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     | Reporting group        |
| Number of subjects analysed              | 24 <sup>[22]</sup>  | 16 <sup>[23]</sup>  | 16 <sup>[24]</sup>  | 16 <sup>[25]</sup>     |
| Units: ng/mL                             |                     |                     |                     |                        |
| geometric mean (confidence interval 95%) |                     |                     |                     |                        |
| 0 h                                      | 26.5 (21.0 to 33.5) | 35.0 (27.4 to 44.7) | 40.3 (28.4 to 57.2) | 28.4 (19.6 to 41.2)    |
| 2 h                                      | 24.4 (20.2 to 29.5) | 5.1 (4.5 to 5.7)    | 3.7 (3.1 to 4.4)    | 4.0 (3.5 to 4.6)       |
| 6 h                                      | 26.0 (21.0 to 32.2) | 7.9 (7.0 to 8.8)    | 5.0 (4.2 to 5.9)    | 5.6 (4.8 to 6.7)       |
| 12 h                                     | 24.5 (19.6 to 30.6) | 9.9 (8.4 to 11.6)   | 5.7 (4.7 to 6.9)    | 6.3 (5.4 to 7.4)       |
| 24 h                                     | 26.5 (21.4 to 32.9) | 8.1 (6.8 to 9.7)    | 7.6 (6.0 to 9.7)    | 7.4 (6.2 to 8.7)       |
| 72 h                                     | 26.6 (21.7 to 32.6) | 20.6 (15.4 to 27.5) | 7.3 (5.9 to 9.1)    | 6.9 (5.8 to 8.2)       |
| Day 5                                    | 27.3 (22.9 to 32.6) | 36.0 (24.5 to 52.9) | 12.4 (9.6 to 16.0)  | 6.8 (5.6 to 8.2)       |
| Day 8                                    | 29.2 (23.9 to 35.6) | 40.0 (27.0 to 59.1) | 35.9 (19.8 to 65.3) | 13.2 (10.6 to 16.4)    |
| Day 13                                   | 32.9 (24.8 to 43.5) | 40.2 (25.7 to 62.9) | 40.2 (24.1 to 67.1) | 22.7 (15.8 to 32.6)    |
| Day 28                                   | 32.2 (23.2 to 44.5) | 42.1 (15.7 to 112)  | 56.6 (22.6 to 142)  | 36.3 (20.7 to 63.9)    |
| Hospital discharge                       | 24.8 (19.8 to 31.2) | 36.7 (18.7 to 72.0) | 20.7 (1.7 to 248)   | 19.7 (-99999 to 99999) |

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

### Statistical analyses

No statistical analyses for this end point

**Primary: Relative change of C5a level**

|   |  |
|---|--|
| End point title   | Relative change of C5a level <sup>[26]</sup> |
| End point description:  |  |
| Relative change of C5a level compared to baseline by time point (FAS).<br>The number of subjects analysed varied between time points. |  |
| End point type  | Primary                                      |
| End point timeframe:  |  |
| At 2 hours (h), 6h, 12h, 24h, 72h, Day 5, Day 8, Day 13, Day 28 after first infusion of IFX-1 or placebo and at hospital discharge    |  |

Notes:

[26] - 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: Only descriptive analyses were defined and performed.

| End point values                      | Placebo Combined   | Verum Cohort 1     | Verum Cohort 2     | Verum Cohort 3         |
|---------------------------------------|--------------------|--------------------|--------------------|------------------------|
| Subject group type                    | Reporting group    | Reporting group    | Reporting group    | Reporting group        |
| Number of subjects analysed           | 24 <sup>[27]</sup> | 16 <sup>[28]</sup> | 16 <sup>[29]</sup> | 16 <sup>[30]</sup>     |
| Units: Percentage                     |                    |                    |                    |                        |
| median (inter-quartile range (Q1-Q3)) |                    |                    |                    |                        |
| 2 h                                   | -7.9 (-18 to 4)    | -83.9 (-90 to -79) | -90.7 (-94 to -86) | -88.6 (-92 to -73)     |
| 6 h                                   | -3.3 (-9 to 3)     | -73.8 (-83 to -70) | -87.6 (-91 to -81) | -81.6 (-89 to -69)     |
| 12 h                                  | -6.3 (-14 to 5)    | -70.0 (-81 to -58) | -84.5 (-90 to -79) | -76.5 (-88 to -66)     |
| 24 h                                  | -1.5 (-16 to 14)   | -77.4 (-85 to -61) | -78.9 (-87 to -73) | -72.1 (-85 to -64)     |
| 72 h                                  | -5.3 (-16 to 6)    | -39.9 (-54 to -18) | -78.8 (-86 to -71) | -74.2 (-86 to -64)     |
| Day 5                                 | -6.8 (-11 to 18)   | 14.0 (-13 to 40)   | -67.1 (-78 to -58) | -73.4 (-86 to -57)     |
| Day 8                                 | 8.2 (-10 to 37)    | 21.4 (-11 to 38)   | -16.3 (-53 to 33)  | -56.7 (-74 to -15)     |
| Day 13                                | 10.8 (3 to 56)     | 1.5 (-24 to 42)    | -9.3 (-37 to -1)   | -5.0 (-33 to 30)       |
| Day 28                                | 24.0 (9 to 52)     | 39.7 (-20 to 107)  | -18.3 (-36 to -11) | 20.8 (6 to 40)         |
| Hospital discharge                    | 36.3 (8 to 46)     | 13.8 (-19 to 36)   | -23.5 (-52 to 69)  | -76.1 (-76.1 to -76.1) |

Notes:

[27] - FAS

[28] - FAS

[29] - FAS

[30] - FAS

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dosing at Day 0 (0h) until Day 28 or hospital discharge, if prior to Day 28. In some cases of prolonged hospital stay after study completion but before database lock, occurrences of adverse events were also reported.

Adverse event reporting additional description:

Safety Analysis Set: All subjects who were randomized and who received any amount of IFX-1 or placebo.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Intravenous administration of placebo in any of the three cohorts corresponding to the Verum Cohorts 1, 2 and 3. The ratio between IFX-1 and placebo within one dose cohort was 2:1. One patient completed the study at Day 28 after first treatment but stayed in hospital and had a serious fatal adverse event 4 weeks after study completion.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Verum Cohort 1 |
|-----------------------|----------------|

Reporting group description:

Intravenous administration of IFX-1 according to the following schedule: 2 x 2 mg/kg body weight (b.w.) on 0 h and 12 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Verum Cohort 2 |
|-----------------------|----------------|

Reporting group description:

Intravenous administration of IFX-1 according to the following schedule: 2 x 4 mg/kg body weight (b.w.) on 0 h and 24 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Verum Cohort 3 |
|-----------------------|----------------|

Reporting group description:

Intravenous administration of IFX-1 according to the following schedule: 3 x 4 mg/kg body weight (b.w.) on 0 h, 24 h and 72 h. For subjects weighing more than 100 kg the dose calculation was based on 100 kg b.w.

| Serious adverse events                            | Placebo Combined                    | Verum Cohort 1   | Verum Cohort 2  |
|---|-------------------------------------|------------------|-----------------|
| Total subjects affected by serious adverse events |                                     |                  |                 |
| subjects affected / exposed                       | 13 / 24 (54.17%)                    | 10 / 16 (62.50%) | 6 / 16 (37.50%) |
| number of deaths (all causes)                     | 4                                   | 6                | 3               |
| number of deaths resulting from adverse events    | 4                                   | 6                | 3               |
| Vascular disorders                                |                                     |                  |                 |
| Hypotension                                       | Additional description: Hypotension |                  |                 |
| subjects affected / exposed                       | 1 / 24 (4.17%)                      | 0 / 16 (0.00%)   | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all   | 0 / 1                               | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all        | 0 / 0                               | 0 / 0            | 0 / 0           |

|  |   |                 |                |
|--|---|-----------------|----------------|
| Hypovolaemic shock<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Hypovolaemic shock                    |                 |                |
|  | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 0   | 0 / 1           | 0 / 0          |
|  | 0 / 0   | 0 / 0           | 0 / 0          |
| Peripheral ischaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Peripheral ischaemia                  |                 |                |
|  | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 1 / 1   | 0 / 0           | 0 / 0          |
|  | 0 / 0   | 0 / 0           | 0 / 0          |
| Shock haemorrhagic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Shock haemorrhagic                    |                 |                |
|  | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 0   | 0 / 1           | 0 / 0          |
|  | 0 / 0   | 0 / 1           | 0 / 0          |
| General disorders and administration site conditions<br>Impaired healing<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | Additional description: Impaired healing                      |                 |                |
|  | 2 / 24 (8.33%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0 / 2   | 0 / 0           | 0 / 0          |
|  | 0 / 1   | 0 / 0           | 0 / 0          |
| Multi-organ failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | Additional description: Multi-organ failure                   |                 |                |
|  | 2 / 24 (8.33%)  | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
|  | 0 / 2   | 0 / 2           | 0 / 0          |
|  | 0 / 2   | 0 / 1           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders<br>Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Chronic obstructive pulmonary disease |                 |                |
|  | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0 / 1   | 0 / 0           | 0 / 0          |
|  | 0 / 0   | 0 / 0           | 0 / 0          |
| Pleural effusion<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Pleural effusion                      |                 |                |
|  | 1 / 24 (4.17%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 1   | 0 / 1           | 0 / 0          |
|  | 0 / 0   | 0 / 0           | 0 / 0          |
| Pulmonary embolism   | Additional description: Pulmonary embolism                    |                 |                |
|  |   |                 |                |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Respiratory failure                             | Additional description: Respiratory failure               |                 |                 |
| subjects affected / exposed                     | 4 / 24 (16.67%)   | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences causally related to treatment / all | 0 / 4   | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |   |                 |                 |
| Sopor   | Additional description: Sopor                             |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Investigations                                  |   |                 |                 |
| Inflammatory marker increased                   | Additional description: Inflammatory marker increased     |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |   |                 |                 |
| Anastomotic leak                                | Additional description: Anastomotic leak                  |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 1           |
| Gastrointestinal anastomotic leak               | Additional description: Gastrointestinal anastomotic leak |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Hepatic rupture                                 | Additional description: Hepatic rupture                   |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Post procedural haemorrhage                     | Additional description: Post procedural haemorrhage       |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |



|   |   |                |                |
|---|---|----------------|----------------|
| Suture related complication<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | Additional description: Suture related complication     |                |                |
|   | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Vena cava injury<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Vena cava injury                |                |                |
|   | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
|   | 0 / 0   | 0 / 1          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all          | Additional description: Atrial fibrillation             |                |                |
|   | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
|   | 0 / 0   | 0 / 0          | 1 / 1          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Cardiac arrest<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                    | Additional description: Cardiac arrest                  |                |                |
|   | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
|   | 0 / 0   | 0 / 1          | 0 / 1          |
|   | 0 / 0   | 0 / 1          | 0 / 1          |
| Cardiomyopathy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                    | Additional description: Cardiomyopathy                  |                |                |
|   | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | Additional description: Tachyarrhythmia                 |                |                |
|   | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
|   | 0 / 0   | 0 / 1          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Nervous system disorders<br>Cerebellar infarction<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Cerebellar infarction           |                |                |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
|   | 0 / 1   | 0 / 0          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |
| Critical illness polyneuropathy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                   | Additional description: Critical illness polyneuropathy |                |                |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
|   | 0 / 1   | 0 / 0          | 0 / 0          |
|   | 0 / 0   | 0 / 0          | 0 / 0          |

|   |   |                |                |
|---|---|----------------|----------------|
| Eye disorders                                   |   |                |                |
| Diplopia  | Additional description: Diplopia                    |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |   |                |                |
| Gastric perforation                             | Additional description: Gastric perforation         |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Gastrointestinal fistula                        | Additional description: Gastrointestinal fistula    |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0          | 0 / 0          |
| Ileus   | Additional description: Ileus                       |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Intestinal ischaemia                            | Additional description: Intestinal ischaemia        |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1          | 0 / 1          |
| Intestinal perforation                          | Additional description: Intestinal perforation      |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Intra-abdominal haemorrhage                     | Additional description: Intra-abdominal haemorrhage |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Large intestine perforation                     | Additional description: Large intestine perforation |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |

|  |  |                 |                |
|--|--|-----------------|----------------|
| Pancreatitis necrotising<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | Additional description: Pancreatitis necrotising           |                 |                |
|  | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0 / 2  | 0 / 0           | 0 / 0          |
|  | 0 / 1  | 0 / 0           | 0 / 0          |
| Small intestinal perforation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | Additional description: Small intestinal perforation       |                 |                |
|  | 1 / 24 (4.17%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 1  | 0 / 1           | 0 / 0          |
|  | 0 / 1  | 0 / 0           | 0 / 0          |
| Upper gastrointestinal haemorrhage<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | Additional description: Upper gastrointestinal haemorrhage |                 |                |
|  | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0 / 0  | 0 / 0           | 0 / 0          |
|  | 0 / 0  | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders<br>Acute hepatic failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Acute hepatic failure              |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 0  | 1 / 1           | 0 / 0          |
|  | 0 / 0  | 1 / 1           | 0 / 0          |
| Hepatic haematoma<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Hepatic haematoma                  |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0 / 0  | 0 / 1           | 0 / 0          |
|  | 0 / 0  | 0 / 0           | 0 / 0          |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Acute kidney injury                |                 |                |
|  | 0 / 24 (0.00%)   | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
|  | 0 / 0  | 0 / 2           | 0 / 0          |
|  | 0 / 0  | 0 / 1           | 0 / 0          |
| Infections and infestations<br>Abdominal infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Abdominal infection                |                 |                |
|  | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0 / 1  | 0 / 0           | 0 / 0          |
|  | 0 / 0  | 0 / 0           | 0 / 0          |
| Abdominal wall abscess   | Additional description: Abdominal wall abscess             |                 |                |

|   |   |                |                |
|---|---|----------------|----------------|
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Appendicitis                                    | Additional description: Appendicitis                |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0          | 0 / 0          |
| Cholecystitis infective                         | Additional description: Cholecystitis infective     |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Endocarditis                                    | Additional description: Endocarditis                |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                                      | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Gastroenteritis clostridial                     | Additional description: Gastroenteritis clostridial |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Infection                                       | Additional description: Infection                   |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0          | 0 / 0          |
| Peritonitis                                     | Additional description: Peritonitis                 |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                                      | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          | 0 / 0          |
| Pneumonia                                       | Additional description: Pneumonia                   |                |                |
| subjects affected / exposed                     | 2 / 24 (8.33%)                                      | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 1          | 0 / 0          |
| Sepsis  | Additional description: Sepsis                      |                |                |

|   |   |                 |                |
|---|---|-----------------|----------------|
| subjects affected / exposed                     | 1 / 24 (4.17%)                          | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           | 0 / 0          |
| Septic shock                                    | Additional description: Septic shock    |                 |                |
| subjects affected / exposed                     | 4 / 24 (16.67%)                         | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 5                                   | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 2                                   | 0 / 0           | 0 / 1          |
| Metabolism and nutrition disorders              |   |                 |                |
| Hyperkalaemia                                   | Additional description: Hyperkalaemia   |                 |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                          | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 2           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 1           | 0 / 1          |
| Hypervolaemia                                   | Additional description: Hypervolaemia   |                 |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)                          | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           | 0 / 0          |
| Hypocalcaemia                                   | Additional description: Hypocalcaemia   |                 |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                          | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           | 0 / 1          |
| Lactic acidosis                                 | Additional description: Lactic acidosis |                 |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)                          | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0           | 0 / 1          |

|   |                                     |  |  |
|---|-------------------------------------|--|--|
| <b>Serious adverse events</b>                     | Verum Cohort 3                      |  |  |
| Total subjects affected by serious adverse events |                                     |  |  |
| subjects affected / exposed                       | 7 / 16 (43.75%)                     |  |  |
| number of deaths (all causes)                     | 2                                   |  |  |
| number of deaths resulting from adverse events    | 2                                   |  |  |
| Vascular disorders                                |                                     |  |  |
| Hypotension                                       | Additional description: Hypotension |  |  |
| subjects affected / exposed                       | 0 / 16 (0.00%)                      |  |  |
| occurrences causally related to treatment / all   | 0 / 0                               |  |  |
| deaths causally related to treatment / all        | 0 / 0                               |  |  |

|  |   |  |  |
|--|---|--|--|
| Hypovolaemic shock<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Hypovolaemic shock                    |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| Peripheral ischaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Peripheral ischaemia                  |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| Shock haemorrhagic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Shock haemorrhagic                    |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| General disorders and administration site conditions<br>Impaired healing<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | Additional description: Impaired healing                      |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| Multi-organ failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | Additional description: Multi-organ failure                   |  |  |
|  | 1 / 16 (6.25%)  |  |  |
|  | 0 / 1   |  |  |
|  | 0 / 0   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Chronic obstructive pulmonary disease |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Pleural effusion                      |  |  |
|  | 0 / 16 (0.00%)  |  |  |
|  | 0 / 0   |  |  |
|  | 0 / 0   |  |  |
| Pulmonary embolism   | Additional description: Pulmonary embolism                    |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Respiratory failure                             | Additional description: Respiratory failure               |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Psychiatric disorders                           |   |  |  |
| Sopor   | Additional description: Sopor                             |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Investigations                                  |   |  |  |
| Inflammatory marker increased                   | Additional description: Inflammatory marker increased     |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Injury, poisoning and procedural complications  |   |  |  |
| Anastomotic leak                                | Additional description: Anastomotic leak                  |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Gastrointestinal anastomotic leak               | Additional description: Gastrointestinal anastomotic leak |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Hepatic rupture                                 | Additional description: Hepatic rupture                   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Post procedural haemorrhage                     | Additional description: Post procedural haemorrhage       |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|   |   |  |  |
|---|---|--|--|
| Suture related complication<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                       | Additional description: Suture related complication     |  |  |
|   | 1 / 16 (6.25%)  |  |  |
|   | 0 / 1   |  |  |
|   | 0 / 0   |  |  |
| Vena cava injury<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                                  | Additional description: Vena cava injury                |  |  |
|   | 0 / 16 (0.00%)  |  |  |
|   | 0 / 0   |  |  |
|   | 0 / 0   |  |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all          | Additional description: Atrial fibrillation             |  |  |
|   | 0 / 16 (0.00%)  |  |  |
|   | 0 / 0   |  |  |
|   | 0 / 0   |  |  |
| Cardiac arrest<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                                    | Additional description: Cardiac arrest                  |  |  |
|   | 1 / 16 (6.25%)  |  |  |
|   | 0 / 1   |  |  |
|   | 0 / 1   |  |  |
| Cardiomyopathy<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                                    | Additional description: Cardiomyopathy                  |  |  |
|   | 1 / 16 (6.25%)  |  |  |
|   | 0 / 1   |  |  |
|   | 0 / 1   |  |  |
| Tachyarrhythmia<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                                   | Additional description: Tachyarrhythmia                 |  |  |
|   | 0 / 16 (0.00%)  |  |  |
|   | 0 / 0   |  |  |
|   | 0 / 0   |  |  |
| Nervous system disorders<br>Cerebellar infarction<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all | Additional description: Cerebellar infarction           |  |  |
|   | 0 / 16 (0.00%)  |  |  |
|   | 0 / 0   |  |  |
|   | 0 / 0   |  |  |
| Critical illness polyneuropathy<br>subjects affected / exposed<br><br>occurrences causally related to<br>treatment / all<br><br>deaths causally related to<br>treatment / all                   | Additional description: Critical illness polyneuropathy |  |  |
|   | 0 / 16 (0.00%)  |  |  |
|   | 0 / 0   |  |  |
|   | 0 / 0   |  |  |



|   |   |  |  |
|---|---|--|--|
| Eye disorders                                   |   |  |  |
| Diplopia  | Additional description: Diplopia                    |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastrointestinal disorders                      |   |  |  |
| Gastric perforation                             | Additional description: Gastric perforation         |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastrointestinal fistula                        | Additional description: Gastrointestinal fistula    |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Ileus   | Additional description: Ileus                       |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Intestinal ischaemia                            | Additional description: Intestinal ischaemia        |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Intestinal perforation                          | Additional description: Intestinal perforation      |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Intra-abdominal haemorrhage                     | Additional description: Intra-abdominal haemorrhage |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Large intestine perforation                     | Additional description: Large intestine perforation |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|  |  |  |  |
|--|--|--|--|
| Pancreatitis necrotising<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | Additional description: Pancreatitis necrotising           |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Small intestinal perforation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | Additional description: Small intestinal perforation       |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Upper gastrointestinal haemorrhage<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | Additional description: Upper gastrointestinal haemorrhage |  |  |
|  | 1 / 16 (6.25%)   |  |  |
|  | 0 / 1  |  |  |
|  | 0 / 0  |  |  |
| Hepatobiliary disorders<br>Acute hepatic failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | Additional description: Acute hepatic failure              |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Hepatic haematoma<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Hepatic haematoma                  |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Acute kidney injury                |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Infections and infestations<br>Abdominal infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Abdominal infection                |  |  |
|  | 0 / 16 (0.00%)   |  |  |
|  | 0 / 0  |  |  |
|  | 0 / 0  |  |  |
| Abdominal wall abscess   | Additional description: Abdominal wall abscess             |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Appendicitis                                    | Additional description: Appendicitis                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Cholecystitis infective                         | Additional description: Cholecystitis infective     |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Endocarditis                                    | Additional description: Endocarditis                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastroenteritis clostridial                     | Additional description: Gastroenteritis clostridial |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Infection                                       | Additional description: Infection                   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Peritonitis                                     | Additional description: Peritonitis                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Pneumonia                                       | Additional description: Pneumonia                   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                                      |  |  |
| occurrences causally related to treatment / all | 0 / 0   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Sepsis  | Additional description: Sepsis                      |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 0                                   |  |  |
| deaths causally related to treatment / all      | 0 / 0                                   |  |  |
| Septic shock                                    | Additional description: Septic shock    |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 1                                   |  |  |
| deaths causally related to treatment / all      | 0 / 1                                   |  |  |
| Metabolism and nutrition disorders              |   |  |  |
| Hyperkalaemia                                   | Additional description: Hyperkalaemia   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 0                                   |  |  |
| deaths causally related to treatment / all      | 0 / 0                                   |  |  |
| Hypervolaemia                                   | Additional description: Hypervolaemia   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 0                                   |  |  |
| deaths causally related to treatment / all      | 0 / 0                                   |  |  |
| Hypocalcaemia                                   | Additional description: Hypocalcaemia   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 0                                   |  |  |
| deaths causally related to treatment / all      | 0 / 0                                   |  |  |
| Lactic acidosis                                 | Additional description: Lactic acidosis |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)                          |  |  |
| occurrences causally related to treatment / all | 0 / 0                                   |  |  |
| deaths causally related to treatment / all      | 0 / 0                                   |  |  |

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

| Non-serious adverse events                            | Placebo Combined                     | Verum Cohort 1   | Verum Cohort 2   |
|---|--------------------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                                      |                  |                  |
| subjects affected / exposed                           | 20 / 24 (83.33%)                     | 13 / 16 (81.25%) | 10 / 16 (62.50%) |
| Vascular disorders                                    |                                      |                  |                  |
| Haemorrhage   | Additional description: Haemorrhage  |                  |                  |
| subjects affected / exposed                           | 0 / 24 (0.00%)                       | 1 / 16 (6.25%)   | 0 / 16 (0.00%)   |
| occurrences (all)                                     | 0                                    | 1                | 0                |
| Hypertension  | Additional description: Hypertension |                  |                  |

|  |  |                |                |
|--|--|----------------|----------------|
| subjects affected / exposed                          | 2 / 24 (8.33%)   | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 2  | 0              | 1              |
| Hypotension  | Additional description: Hypotension                    |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0  | 1              | 0              |
| Jugular vein thrombosis                              | Additional description: Jugular vein thrombosis        |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 0  | 0              | 1              |
| Poor peripheral circulation                          | Additional description: Poor peripheral circulation    |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 0  | 0              | 1              |
| Surgical and medical procedures                      |  |                |                |
| Endotracheal intubation                              | Additional description: Endotracheal intubation        |                |                |
| subjects affected / exposed                          | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1  | 0              | 0              |
| General disorders and administration site conditions |  |                |                |
| Asthenia   | Additional description: Asthenia                       |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0  | 0              | 0              |
| Catheter site hypersensitivity                       | Additional description: Catheter site hypersensitivity |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0  | 0              | 0              |
| Generalised oedema                                   | Additional description: Generalised oedema             |                |                |
| subjects affected / exposed                          | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1  | 0              | 0              |
| Hyperpyrexia   | Additional description: Hyperpyrexia                   |                |                |
| subjects affected / exposed                          | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1  | 0              | 0              |
| Hyperthermia   | Additional description: Hyperthermia                   |                |                |
| subjects affected / exposed                          | 2 / 24 (8.33%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 2  | 0              | 0              |
| Impaired healing                                     | Additional description: Impaired healing               |                |                |
| subjects affected / exposed                          | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0  | 1              | 0              |
| Injection site haematoma                             | Additional description: Injection site haematoma       |                |                |

|   |   |                |                |
|---|---|----------------|----------------|
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1   | 0              | 0              |
| Malaise   | Additional description: Malaise                             |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1   | 0              | 0              |
| Oedema  | Additional description: Oedema                              |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1   | 1              | 0              |
| Oedema peripheral                               | Additional description: Oedema peripheral                   |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1   | 0              | 0              |
| Pyrexia   | Additional description: Pyrexia                             |                |                |
| subjects affected / exposed                     | 3 / 24 (12.50%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 3   | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |   |                |                |
| Acute respiratory distress syndrome             | Additional description: Acute respiratory distress syndrome |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0   | 0              | 0              |
| Bronchial obstruction                           | Additional description: Bronchial obstruction               |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                               | 0   | 0              | 1              |
| Cough   | Additional description: Cough                               |                |                |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1   | 0              | 0              |
| Epistaxis                                       | Additional description: Epistaxis                           |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0   | 0              | 0              |
| Hypercapnia                                     | Additional description: Hypercapnia                         |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0   | 0              | 0              |
| Hypoventilation                                 | Additional description: Hypoventilation                     |                |                |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                               | 0   | 0              | 1              |
| Pleural effusion                                | Additional description: Pleural effusion                    |                |                |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 1   | 2               | 2               |
| Pneumothorax                                    | Additional description: Pneumothorax                                    |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1   | 0               | 0               |
| Pulmonary oedema                                | Additional description: Pulmonary oedema                                |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0   | 0               | 1               |
| Respiration abnormal                            | Additional description: Respiration abnormal                            |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0   | 1               | 0               |
| Respiratory failure                             | Additional description: Respiratory failure                             |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1   | 1               | 0               |
| Psychiatric disorders                           |   |                 |                 |
| Agitation                                       | Additional description: Agitation                                       |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0   | 0               | 2               |
| Delirium  | Additional description: Delirium  |                 |                 |
| subjects affected / exposed                     | 4 / 24 (16.67%)   | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 4   | 2               | 2               |
| Depression                                      | Additional description: Depression                                      |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1   | 0               | 0               |
| Restlessness                                    | Additional description: Restlessness                                    |                 |                 |
| subjects affected / exposed                     | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1   | 0               | 0               |
| Sopor   | Additional description: Sopor   |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0   | 1               | 0               |
| Investigations                                  |   |                 |                 |
| Activated partial thromboplastin time prolonged | Additional description: Activated partial thromboplastin time prolonged |                 |                 |
| subjects affected / exposed                     | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0   | 1               | 0               |
| Blood bilirubin increased                       | Additional description: Blood bilirubin increased                       |                 |                 |

|                                       |   |                 |                |
|---------------------------------------|---|-----------------|----------------|
| subjects affected / exposed           | 1 / 24 (4.17%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 1               | 0              |
| Blood creatinine increased            | Additional description: Blood creatinine increased            |                 |                |
| subjects affected / exposed           | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                     | 0   | 0               | 1              |
| Blood lactate dehydrogenase increased | Additional description: Blood lactate dehydrogenase increased |                 |                |
| subjects affected / exposed           | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 0   | 1               | 0              |
| Blood potassium decreased             | Additional description: Blood potassium decreased             |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 0               | 0              |
| Blood urea increased                  | Additional description: Blood urea increased                  |                 |                |
| subjects affected / exposed           | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                     | 0   | 0               | 1              |
| Body temperature decreased            | Additional description: Body temperature decreased            |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 0               | 0              |
| Body temperature increased            | Additional description: Body temperature increased            |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 3               | 0              |
| Glutamate dehydrogenase increased     | Additional description: Glutamate dehydrogenase increased     |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 0               | 0              |
| Haematocrit decreased                 | Additional description: Haematocrit decreased                 |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 1   | 0               | 0              |
| Haemoglobin decreased                 | Additional description: Haemoglobin decreased                 |                 |                |
| subjects affected / exposed           | 6 / 24 (25.00%)   | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all)                     | 8   | 3               | 1              |
| Hepatic enzyme increased              | Additional description: Hepatic enzyme increased              |                 |                |
| subjects affected / exposed           | 1 / 24 (4.17%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%) |
| occurrences (all)                     | 1   | 1               | 1              |
| Lipase increased                      | Additional description: Lipase increased                      |                 |                |
| subjects affected / exposed           | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                     | 0   | 0               | 0              |



|  |  |                 |                 |
|--|--|-----------------|-----------------|
| Myocardial necrosis marker increased           | Additional description: Myocardial necrosis marker increased |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 0  | 1               | 0               |
| Myoglobin blood increased                      | Additional description: Myoglobin blood increased            |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                              | 0  | 0               | 1               |
| Oxygen saturation decreased                    | Additional description: Oxygen saturation decreased          |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 0  | 1               | 0               |
| PaO2/FIO2 ratio decreased                      | Additional description: PaO2/FIO2 ratio decreased            |                 |                 |
| subjects affected / exposed                    | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 1  | 0               | 0               |
| Platelet count decreased                       | Additional description: Platelet count decreased             |                 |                 |
| subjects affected / exposed                    | 3 / 24 (12.50%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 3  | 0               | 0               |
| Platelet count increased                       | Additional description: Platelet count increased             |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 0  | 0               | 0               |
| Transaminases increased                        | Additional description: Transaminases increased              |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all)                              | 0  | 2               | 2               |
| Injury, poisoning and procedural complications |  |                 |                 |
| Endotracheal intubation complication           | Additional description: Endotracheal intubation complication |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 0  | 1               | 0               |
| Post procedural bile leak                      | Additional description: Post procedural bile leak            |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                              | 0  | 0               | 1               |
| Post procedural complication                   | Additional description: Post procedural complication         |                 |                 |
| subjects affected / exposed                    | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 1  | 0               | 0               |
| Post procedural haemorrhage                    | Additional description: Post procedural haemorrhage          |                 |                 |
| subjects affected / exposed                    | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                              | 0  | 1               | 0               |
| Psychosis postoperative                        | Additional description: Psychosis postoperative              |                 |                 |

|                                |  |                |                 |
|--------------------------------|--|----------------|-----------------|
| subjects affected / exposed    | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 1  | 0              | 0               |
| Seroma                         | Additional description: Seroma                         |                |                 |
| subjects affected / exposed    | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 1  | 0              | 0               |
| Shunt thrombosis               | Additional description: Shunt thrombosis               |                |                 |
| subjects affected / exposed    | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 1  | 0              | 0               |
| Wound secretion                | Additional description: Wound secretion                |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 1              | 0               |
| Cardiac disorders              |  |                |                 |
| Arrhythmia                     | Additional description: Arrhythmia                     |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 1              | 0               |
| Atrial fibrillation            | Additional description: Atrial fibrillation            |                |                 |
| subjects affected / exposed    | 3 / 24 (12.50%)  | 1 / 16 (6.25%) | 1 / 16 (6.25%)  |
| occurrences (all)              | 4  | 1              | 1               |
| Atrial flutter                 | Additional description: Atrial flutter                 |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 0              | 0               |
| Bradycardia                    | Additional description: Bradycardia                    |                |                 |
| subjects affected / exposed    | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all)              | 1  | 0              | 2               |
| Cardiac arrest                 | Additional description: Cardiac arrest                 |                |                 |
| subjects affected / exposed    | 1 / 24 (4.17%)   | 0 / 16 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)              | 1  | 0              | 3               |
| Myocardial ischaemia           | Additional description: Myocardial ischaemia           |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 0              | 0               |
| Supraventricular extrasystoles | Additional description: Supraventricular extrasystoles |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 1              | 0               |
| Supraventricular tachycardia   | Additional description: Supraventricular tachycardia   |                |                 |
| subjects affected / exposed    | 0 / 24 (0.00%)   | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)              | 0  | 1              | 0               |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all) | Additional description: Tachyarrhythmia                 |                 |                 |
|   | 5 / 24 (20.83%)   | 2 / 16 (12.50%) | 0 / 16 (0.00%)  |
|   | 6   | 2               | 0               |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Tachycardia                     |                 |                 |
|   | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
|   | 0   | 1               | 1               |
| Nervous system disorders  |   |                 |                 |
|   | Additional description: Critical illness polyneuropathy |                 |                 |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
|   | 1   | 0               | 0               |
|   | Additional description: Disturbance in attention        |                 |                 |
|   | 1 / 24 (4.17%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
|   | 1   | 1               | 0               |
|   | Additional description: Epilepsy                        |                 |                 |
|   | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
|   | 0   | 0               | 0               |
|   | Additional description: Headache                        |                 |                 |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
|   | 1   | 0               | 0               |
|   | Additional description: Hypertonia                      |                 |                 |
|   | 0 / 24 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
|   | 0   | 1               | 0               |
|   | Additional description: Polyneuropathy                  |                 |                 |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
|   | 1   | 0               | 0               |
|   | Additional description: Seizure                         |                 |                 |
|   | 0 / 24 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
|   | 0   | 0               | 1               |
| Blood and lymphatic system disorders                                |   |                 |                 |
|   | Additional description: Anaemia                         |                 |                 |
|   | 3 / 24 (12.50%)   | 2 / 16 (12.50%) | 6 / 16 (37.50%) |
|   | 3   | 2               | 7               |
|   | Additional description: Coagulopathy                    |                 |                 |
|   | 1 / 24 (4.17%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
|   | 1   | 0               | 0               |
|   | Additional description: Haemorrhagic anaemia            |                 |                 |

|                                    |  |                 |                 |
|------------------------------------|--|-----------------|-----------------|
| subjects affected / exposed        | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0  | 1               | 0               |
| Leukocytosis                       | Additional description: Leukocytosis                       |                 |                 |
| subjects affected / exposed        | 3 / 24 (12.50%)  | 2 / 16 (12.50%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 3  | 2               | 0               |
| Leukopenia                         | Additional description: Leukopenia                         |                 |                 |
| subjects affected / exposed        | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0  | 0               | 0               |
| Thrombocytopenia                   | Additional description: Thrombocytopenia                   |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 2 / 16 (12.50%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1  | 2               | 0               |
| Thrombocytosis                     | Additional description: Thrombocytosis                     |                 |                 |
| subjects affected / exposed        | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                  | 0  | 0               | 1               |
| Gastrointestinal disorders         |  |                 |                 |
| Abdominal pain                     | Additional description: Abdominal pain                     |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1  | 0               | 0               |
| Ascites                            | Additional description: Ascites                            |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1  | 0               | 0               |
| Constipation                       | Additional description: Constipation                       |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1  | 0               | 0               |
| Diarrhoea                          | Additional description: Diarrhoea                          |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 2 / 16 (12.50%) |
| occurrences (all)                  | 1  | 0               | 2               |
| Duodenal ulcer                     | Additional description: Duodenal ulcer                     |                 |                 |
| subjects affected / exposed        | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0  | 1               | 0               |
| Gastritis                          | Additional description: Gastritis                          |                 |                 |
| subjects affected / exposed        | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0  | 1               | 0               |
| Gastrointestinal motility disorder | Additional description: Gastrointestinal motility disorder |                 |                 |
| subjects affected / exposed        | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1  | 0               | 0               |

|  |  |                 |                |
|--|--|-----------------|----------------|
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | Additional description: Gastrooesophageal reflux disease |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0  | 1               | 0              |
| Ileus<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Ileus                            |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0  | 1               | 0              |
| Impaired gastric emptying<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Impaired gastric emptying        |                 |                |
|  | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
|  | 0  | 0               | 1              |
| Intra-abdominal haematoma<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Intra-abdominal haematoma        |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 0  | 1               | 0              |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Nausea                           |                 |                |
|  | 2 / 24 (8.33%)   | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
|  | 2  | 2               | 0              |
| Oesophageal haemorrhage<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Oesophageal haemorrhage          |                 |                |
|  | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0  | 0               | 0              |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Rectal haemorrhage               |                 |                |
|  | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 0  | 0               | 0              |
| Small intestinal perforation<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Small intestinal perforation     |                 |                |
|  | 0 / 24 (0.00%)   | 1 / 16 (6.25%)  | 1 / 16 (6.25%) |
|  | 0  | 2               | 1              |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Vomiting                         |                 |                |
|  | 2 / 24 (8.33%)   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
|  | 2  | 1               | 0              |
| Hepatobiliary disorders  |  |                 |                |
| Cholestasis<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Cholestasis                      |                 |                |
|  | 0 / 24 (0.00%)   | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
|  | 0  | 0               | 1              |
| Gallbladder perforation<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Gallbladder perforation          |                 |                |
|  | 1 / 24 (4.17%)   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
|  | 1  | 0               | 0              |
| Hepatic failure  | Additional description: Hepatic failure                  |                 |                |

|  |   |                |                |
|--|---|----------------|----------------|
| subjects affected / exposed            | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 0              | 0              |
| Hepatocellular injury                  | Additional description: Hepatocellular injury         |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 0              | 0              |
| Perforation bile duct                  | Additional description: Perforation bile duct         |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0   | 0              | 1              |
| Skin and subcutaneous tissue disorders |   |                |                |
| Lividity                               | Additional description: Lividity                      |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 1              | 0              |
| Penile ulceration                      | Additional description: Penile ulceration             |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 1              | 0              |
| Rash                                   | Additional description: Rash                          |                |                |
| subjects affected / exposed            | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 1   | 0              | 0              |
| Rash maculo-papular                    | Additional description: Rash maculo-papular           |                |                |
| subjects affected / exposed            | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 1   | 0              | 0              |
| Renal and urinary disorders            |   |                |                |
| Renal impairment                       | Additional description: Renal impairment              |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 1              | 0              |
| Endocrine disorders                    |   |                |                |
| Hypothyroidism                         | Additional description: Hypothyroidism                |                |                |
| subjects affected / exposed            | 2 / 24 (8.33%)  | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 2   | 0              | 1              |
| Infections and infestations            |   |                |                |
| Abdominal abscess                      | Additional description: Abdominal abscess             |                |                |
| subjects affected / exposed            | 0 / 24 (0.00%)  | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0   | 1              | 0              |
| Clostridium difficile colitis          | Additional description: Clostridium difficile colitis |                |                |
| subjects affected / exposed            | 1 / 24 (4.17%)  | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 1   | 0              | 0              |
| Cystitis                               | Additional description: Cystitis                      |                |                |

|                                    |  |                 |                |
|------------------------------------|--|-----------------|----------------|
| subjects affected / exposed        | 0 / 24 (0.00%)                                   | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                  | 0  | 0               | 1              |
| Device related infection           | Additional description: Device related infection |                 |                |
| subjects affected / exposed        | 1 / 24 (4.17%)                                   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1  | 0               | 0              |
| Fungal infection                   | Additional description: Fungal infection         |                 |                |
| subjects affected / exposed        | 0 / 24 (0.00%)                                   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0  | 1               | 0              |
| Otitis media                       | Additional description: Otitis media             |                 |                |
| subjects affected / exposed        | 0 / 24 (0.00%)                                   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0  | 0               | 0              |
| Peritonitis                        | Additional description: Peritonitis              |                 |                |
| subjects affected / exposed        | 0 / 24 (0.00%)                                   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0  | 0               | 0              |
| Pneumonia                          | Additional description: Pneumonia                |                 |                |
| subjects affected / exposed        | 1 / 24 (4.17%)                                   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1  | 1               | 0              |
| Urinary tract infection            | Additional description: Urinary tract infection  |                 |                |
| subjects affected / exposed        | 2 / 24 (8.33%)                                   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 2  | 0               | 0              |
| Metabolism and nutrition disorders |  |                 |                |
| Hyperglycaemia                     | Additional description: Hyperglycaemia           |                 |                |
| subjects affected / exposed        | 3 / 24 (12.50%)                                  | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 3  | 1               | 0              |
| Hyperkalaemia                      | Additional description: Hyperkalaemia            |                 |                |
| subjects affected / exposed        | 2 / 24 (8.33%)                                   | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 2  | 5               | 0              |
| Hypernatraemia                     | Additional description: Hypernatraemia           |                 |                |
| subjects affected / exposed        | 4 / 24 (16.67%)                                  | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all)                  | 4  | 2               | 1              |
| Hyperuricaemia                     | Additional description: Hyperuricaemia           |                 |                |
| subjects affected / exposed        | 1 / 24 (4.17%)                                   | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1  | 0               | 0              |
| Hypoalbuminaemia                   | Additional description: Hypoalbuminaemia         |                 |                |
| subjects affected / exposed        | 2 / 24 (8.33%)                                   | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                  | 2  | 0               | 1              |

|  |  |                     |                      |
|--|--|---------------------|----------------------|
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Hypocalcaemia      |                     |                      |
|  | 0 / 24 (0.00%)<br>0                        | 1 / 16 (6.25%)<br>1 | 1 / 16 (6.25%)<br>1  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Hypoglycaemia      |                     |                      |
|  | 1 / 24 (4.17%)<br>1                        | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Hypokalaemia       |                     |                      |
|  | 3 / 24 (12.50%)<br>3                       | 1 / 16 (6.25%)<br>1 | 2 / 16 (12.50%)<br>2 |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Hyponatraemia      |                     |                      |
|  | 0 / 24 (0.00%)<br>0                        | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Hypophosphataemia  |                     |                      |
|  | 1 / 24 (4.17%)<br>1                        | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  |
| Metabolic acidosis<br>subjects affected / exposed<br>occurrences (all) | Additional description: Metabolic acidosis |                     |                      |
|  | 0 / 24 (0.00%)<br>0                        | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>                     | Verum Cohort 3                                      |  |  |
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 14 / 16 (87.50%)                                    |  |  |
| Vascular disorders                                    |   |  |  |
| Haemorrhage   | Additional description: Haemorrhage                 |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)                                      |  |  |
| occurrences (all)                                     | 1   |  |  |
| Hypertension  | Additional description: Hypertension                |  |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)                                      |  |  |
| occurrences (all)                                     | 0   |  |  |
| Hypotension   | Additional description: Hypotension                 |  |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)                                      |  |  |
| occurrences (all)                                     | 0   |  |  |
| Jugular vein thrombosis                               | Additional description: Jugular vein thrombosis     |  |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)                                      |  |  |
| occurrences (all)                                     | 0   |  |  |
| Poor peripheral circulation                           | Additional description: Poor peripheral circulation |  |  |



|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Surgical and medical procedures                      |  |  |  |
| Endotracheal intubation                              | Additional description: Endotracheal intubation        |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| General disorders and administration site conditions |  |  |  |
| Asthenia   | Additional description: Asthenia                       |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                                    | 1  |  |  |
| Catheter site hypersensitivity                       | Additional description: Catheter site hypersensitivity |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                                    | 1  |  |  |
| Generalised oedema                                   | Additional description: Generalised oedema             |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                                    | 1  |  |  |
| Hyperpyrexia   | Additional description: Hyperpyrexia                   |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Hyperthermia   | Additional description: Hyperthermia                   |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                                    | 1  |  |  |
| Impaired healing                                     | Additional description: Impaired healing               |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Injection site haematoma                             | Additional description: Injection site haematoma       |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Malaise  | Additional description: Malaise                        |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Oedema   | Additional description: Oedema                         |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                                    | 0  |  |  |
| Oedema peripheral                                    | Additional description: Oedema peripheral              |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 2 / 16 (12.50%)   |  |  |
| occurrences (all)                               | 2   |  |  |
| Pyrexia   | Additional description: Pyrexia                             |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Respiratory, thoracic and mediastinal disorders |   |  |  |
| Acute respiratory distress syndrome             | Additional description: Acute respiratory distress syndrome |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                               | 1   |  |  |
| Bronchial obstruction                           | Additional description: Bronchial obstruction               |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Cough   | Additional description: Cough                               |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Epistaxis                                       | Additional description: Epistaxis                           |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                               | 1   |  |  |
| Hypercapnia                                     | Additional description: Hypercapnia                         |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                               | 1   |  |  |
| Hypoventilation                                 | Additional description: Hypoventilation                     |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Pleural effusion                                | Additional description: Pleural effusion                    |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                               | 1   |  |  |
| Pneumothorax                                    | Additional description: Pneumothorax                        |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Pulmonary oedema                                | Additional description: Pulmonary oedema                    |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Respiration abnormal                            | Additional description: Respiration abnormal                |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Respiratory failure                             | Additional description: Respiratory failure                             |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Psychiatric disorders                           |   |  |  |
| Agitation                                       | Additional description: Agitation                                       |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)   |  |  |
| occurrences (all)                               | 2   |  |  |
| Delirium  | Additional description: Delirium  |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                               | 1   |  |  |
| Depression                                      | Additional description: Depression                                      |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Restlessness                                    | Additional description: Restlessness                                    |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Sopor   | Additional description: Sopor   |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Investigations                                  |   |  |  |
| Activated partial thromboplastin time prolonged | Additional description: Activated partial thromboplastin time prolonged |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Blood bilirubin increased                       | Additional description: Blood bilirubin increased                       |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Blood creatinine increased                      | Additional description: Blood creatinine increased                      |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Blood lactate dehydrogenase increased           | Additional description: Blood lactate dehydrogenase increased           |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                               | 0   |  |  |
| Blood potassium decreased                       | Additional description: Blood potassium decreased                       |  |  |

|                                      |  |  |  |
|--------------------------------------|--|--|--|
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Blood urea increased                 | Additional description: Blood urea increased                 |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Body temperature decreased           | Additional description: Body temperature decreased           |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Body temperature increased           | Additional description: Body temperature increased           |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Glutamate dehydrogenase increased    | Additional description: Glutamate dehydrogenase increased    |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Haematocrit decreased                | Additional description: Haematocrit decreased                |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Haemoglobin decreased                | Additional description: Haemoglobin decreased                |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                    | 1  |  |  |
| Hepatic enzyme increased             | Additional description: Hepatic enzyme increased             |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Lipase increased                     | Additional description: Lipase increased                     |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                    | 1  |  |  |
| Myocardial necrosis marker increased | Additional description: Myocardial necrosis marker increased |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Myoglobin blood increased            | Additional description: Myoglobin blood increased            |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                    | 0  |  |  |
| Oxygen saturation decreased          | Additional description: Oxygen saturation decreased          |  |  |
| subjects affected / exposed          | 2 / 16 (12.50%)  |  |  |
| occurrences (all)                    | 3  |  |  |

|   |  |  |  |
|---|--|--|--|
| PaO2/FIO2 ratio decreased<br>subjects affected / exposed<br>occurrences (all) | Additional description: PaO2/FIO2 ratio decreased            |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Platelet count decreased             |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Platelet count increased             |  |  |
|   | 1 / 16 (6.25%)   |  |  |
|   | 1  |  |  |
|   |  |  |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Transaminases increased              |  |  |
|   | 1 / 16 (6.25%)   |  |  |
|   | 1  |  |  |
|   |  |  |  |
| Injury, poisoning and procedural complications                                |  |  |  |
|   | Additional description: Endotracheal intubation complication |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Post procedural bile leak            |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Post procedural complication         |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Post procedural haemorrhage          |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Psychosis postoperative              |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Seroma                               |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Shunt thrombosis                     |  |  |
|   | 0 / 16 (0.00%)   |  |  |
|   | 0  |  |  |
|   |  |  |  |
|   | Additional description: Wound secretion                      |  |  |
|   |  |  |  |

|                                 |   |  |  |
|---------------------------------|---|--|--|
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Cardiac disorders               |   |  |  |
| Arrhythmia                      | Additional description: Arrhythmia                      |  |  |
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Atrial fibrillation             | Additional description: Atrial fibrillation             |  |  |
| subjects affected / exposed     | 2 / 16 (12.50%)   |  |  |
| occurrences (all)               | 2   |  |  |
| Atrial flutter                  | Additional description: Atrial flutter                  |  |  |
| subjects affected / exposed     | 2 / 16 (12.50%)   |  |  |
| occurrences (all)               | 2   |  |  |
| Bradycardia                     | Additional description: Bradycardia                     |  |  |
| subjects affected / exposed     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)               | 1   |  |  |
| Cardiac arrest                  | Additional description: Cardiac arrest                  |  |  |
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Myocardial ischaemia            | Additional description: Myocardial ischaemia            |  |  |
| subjects affected / exposed     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)               | 1   |  |  |
| Supraventricular extrasystoles  | Additional description: Supraventricular extrasystoles  |  |  |
| subjects affected / exposed     | 1 / 16 (6.25%)  |  |  |
| occurrences (all)               | 1   |  |  |
| Supraventricular tachycardia    | Additional description: Supraventricular tachycardia    |  |  |
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Tachyarrhythmia                 | Additional description: Tachyarrhythmia                 |  |  |
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Tachycardia                     | Additional description: Tachycardia                     |  |  |
| subjects affected / exposed     | 0 / 16 (0.00%)  |  |  |
| occurrences (all)               | 0   |  |  |
| Nervous system disorders        |   |  |  |
| Critical illness polyneuropathy | Additional description: Critical illness polyneuropathy |  |  |

|                                      |  |  |  |
|--------------------------------------|--|--|--|
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Disturbance in attention             | Additional description: Disturbance in attention |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Epilepsy                             | Additional description: Epilepsy                 |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)                                   |  |  |
| occurrences (all)                    | 1  |  |  |
| Headache                             | Additional description: Headache                 |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Hypertonia                           | Additional description: Hypertonia               |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Polyneuropathy                       | Additional description: Polyneuropathy           |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Seizure                              | Additional description: Seizure                  |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Blood and lymphatic system disorders |  |  |  |
| Anaemia                              | Additional description: Anaemia                  |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)                                   |  |  |
| occurrences (all)                    | 1  |  |  |
| Coagulopathy                         | Additional description: Coagulopathy             |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Haemorrhagic anaemia                 | Additional description: Haemorrhagic anaemia     |  |  |
| subjects affected / exposed          | 0 / 16 (0.00%)                                   |  |  |
| occurrences (all)                    | 0  |  |  |
| Leukocytosis                         | Additional description: Leukocytosis             |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)                                   |  |  |
| occurrences (all)                    | 1  |  |  |
| Leukopenia                           | Additional description: Leukopenia               |  |  |
| subjects affected / exposed          | 1 / 16 (6.25%)                                   |  |  |
| occurrences (all)                    | 1  |  |  |

|  |  |  |
|--|--|--|
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Thrombocytopenia                   |  |
|  | 3 / 16 (18.75%)<br>3                                       |  |
| Thrombocytosis<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Thrombocytosis                     |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Gastrointestinal disorders   |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Abdominal pain                     |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Ascites                            |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Constipation                       |  |
|  | 2 / 16 (12.50%)<br>2                                       |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: Diarrhoea                          |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Duodenal ulcer<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: Duodenal ulcer                     |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: Gastritis                          |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Gastrointestinal motility disorder<br>subjects affected / exposed<br>occurrences (all) | Additional description: Gastrointestinal motility disorder |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Gastrooesophageal reflux disease   |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Ileus<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: Ileus                              |  |
|  | 0 / 16 (0.00%)<br>0  |  |
| Impaired gastric emptying  | Additional description: Impaired gastric emptying          |  |



|                              |  |  |  |
|------------------------------|--|--|--|
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |
| Intra-abdominal haematoma    | Additional description: Intra-abdominal haematoma    |  |  |
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |
| Nausea                       | Additional description: Nausea                       |  |  |
| subjects affected / exposed  | 2 / 16 (12.50%)                                      |  |  |
| occurrences (all)            | 2  |  |  |
| Oesophageal haemorrhage      | Additional description: Oesophageal haemorrhage      |  |  |
| subjects affected / exposed  | 1 / 16 (6.25%)                                       |  |  |
| occurrences (all)            | 1  |  |  |
| Rectal haemorrhage           | Additional description: Rectal haemorrhage           |  |  |
| subjects affected / exposed  | 1 / 16 (6.25%)                                       |  |  |
| occurrences (all)            | 1  |  |  |
| Small intestinal perforation | Additional description: Small intestinal perforation |  |  |
| subjects affected / exposed  | 1 / 16 (6.25%)                                       |  |  |
| occurrences (all)            | 1  |  |  |
| Vomiting                     | Additional description: Vomiting                     |  |  |
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |
| Hepatobiliary disorders      |  |  |  |
| Cholestasis                  | Additional description: Cholestasis                  |  |  |
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |
| Gallbladder perforation      | Additional description: Gallbladder perforation      |  |  |
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |
| Hepatic failure              | Additional description: Hepatic failure              |  |  |
| subjects affected / exposed  | 1 / 16 (6.25%)                                       |  |  |
| occurrences (all)            | 1  |  |  |
| Hepatocellular injury        | Additional description: Hepatocellular injury        |  |  |
| subjects affected / exposed  | 1 / 16 (6.25%)                                       |  |  |
| occurrences (all)            | 1  |  |  |
| Perforation bile duct        | Additional description: Perforation bile duct        |  |  |
| subjects affected / exposed  | 0 / 16 (0.00%)                                       |  |  |
| occurrences (all)            | 0  |  |  |

|  |                               |   |  |
|--|-------------------------------|---|--|
| Skin and subcutaneous tissue disorders |                               |   |  |
|  | Lividity                      | Additional description: Lividity                      |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
|  |                               |   |  |
| Penile ulceration                      |                               | Additional description: Penile ulceration             |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
| Rash                                   |                               | Additional description: Rash                          |  |
|  | subjects affected / exposed   | 1 / 16 (6.25%)  |  |
|  | occurrences (all)             | 1   |  |
| Rash maculo-papular                    |                               | Additional description: Rash maculo-papular           |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
| Renal and urinary disorders            |                               |   |  |
|  | Renal impairment              | Additional description: Renal impairment              |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
| Endocrine disorders                    |                               |   |  |
|  | Hypothyroidism                | Additional description: Hypothyroidism                |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
| Infections and infestations            |                               |   |  |
|  | Abdominal abscess             | Additional description: Abdominal abscess             |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
|  |                               |   |  |
|  | Clostridium difficile colitis | Additional description: Clostridium difficile colitis |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
|  |                               |   |  |
|  | Cystitis                      | Additional description: Cystitis                      |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
| Device related infection               |                               |   |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |
| Fungal infection                       |                               | Additional description: Fungal infection              |  |
|  | subjects affected / exposed   | 0 / 16 (0.00%)  |  |
|  | occurrences (all)             | 0   |  |

|   |   |  |
|---|---|--|
| Otitis media<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Otitis media            |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
| Peritonitis<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Peritonitis             |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Pneumonia               |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Urinary tract infection |  |
|   | 0 / 16 (0.00%)                                  |  |
|   | 0   |  |
|   |   |  |
| Metabolism and nutrition disorders  |   |  |
|   | Additional description: Hyperglycaemia          |  |
|   | 2 / 16 (12.50%)                                 |  |
|   | 2   |  |
|   |   |  |
|   | Additional description: Hyperkalaemia           |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
|   | Additional description: Hypernatraemia          |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
|   | Additional description: Hyperuricaemia          |  |
|   | 0 / 16 (0.00%)                                  |  |
|   | 0   |  |
|   |   |  |
|   | Additional description: Hypoalbuminaemia        |  |
|   | 2 / 16 (12.50%)                                 |  |
|   | 2   |  |
|   |   |  |
|   | Additional description: Hypocalcaemia           |  |
|   | 0 / 16 (0.00%)                                  |  |
|   | 0   |  |
|   |   |  |
|   | Additional description: Hypoglycaemia           |  |
|   | 1 / 16 (6.25%)                                  |  |
|   | 1   |  |
|   |   |  |
|   | Additional description: Hypokalaemia            |  |

|                             |  |  |  |
|-----------------------------|--|--|--|
| subjects affected / exposed | 3 / 16 (18.75%)                            |  |  |
| occurrences (all)           | 3  |  |  |
| Hyponatraemia               | Additional description: Hyponatraemia      |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)                             |  |  |
| occurrences (all)           | 0  |  |  |
| Hypophosphataemia           | Additional description: Hypophosphataemia  |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)                             |  |  |
| occurrences (all)           | 0  |  |  |
| Metabolic acidosis          | Additional description: Metabolic acidosis |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)                             |  |  |
| occurrences (all)           | 0  |  |  |

## **More information**

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

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported