



## Clinical trial results:

### Prospective, Randomised, Controlled Phase 2 Study Investigating the Haemostatic Efficacy and Safety of Fibrinogen Concentrate (Octafibrin) and Cryoprecipitate as Fibrinogen Supplementation Sources in Patients Undergoing Cytoreductive Surgery for Pseudomyxoma Peritonei.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-003749-27 |
| Trial protocol           | GB             |
| Global end of trial date | 20 July 2018   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 02 August 2019 |
| First version publication date | 02 August 2019 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | FORMA-05 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Octapharma AG   |
| Sponsor organisation address | Seidenstrasse 2, Lachen, Switzerland, CH-8853                                 |
| Public contact               | Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, sigurd.knaub@octapharma.com |
| Scientific contact           | Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, sigurd.knaub@octapharma.com |

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                       | 19 December 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 20 July 2018     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the overall (i.e. intra- and postoperative) haemostatic efficacy (ability to stop bleeding) of Octafibrin, a human blood-derived protein with that of cryoprecipitate in bleeding patients developing acquired fibrinogen deficiency during removal of tumour growth from the abdomen (cytoreductive surgery) for Pseudomyxoma Peritonei (PMP).

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki.

Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product.

Throughout the study safety was assessed, such as collecting information (e.g., frequency, severity, causality) on adverse events (AEs), treatment-emergent adverse events (TEAEs), serious AEs (SAEs) and adverse drug reactions (ADRs). In addition, monitoring of vital signs, routine clinical laboratory assessment including of coagulation parameters and viral safety testing were performed.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 13 March 2017 |
| 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 | United Kingdom: 45 |
| Worldwide total number of subjects   | 45                 |
| EEA total number of subjects         | 45                 |

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)      | 31 |
| From 65 to 84 years       | 14 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients undergoing cytoreductive surgery for Pseudomyxoma peritonei with need of Fibrinogen supplementation were screened according to predefined in- and exclusion criteria.

### Period 1

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

### Arms

|  |                                   |
|--|-----------------------------------|
| Are arms mutually exclusive?           | Yes                               |
| <b>Arm title</b>                       | Octafibrin                        |
| Arm description: -                     |                                   |
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Octafibrin                        |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Octafibrin was administered by IV injection, using an established IV route. The first dose of Octafibrin (4 g) was pre-emptively administered based on clinical judgement for fibrinogen supplementation made at the 'bleeding risk assessment' time point, which took place approximately 60–90 minutes after the beginning of surgery, before 2 L of blood had been lost.

Further Octafibrin administration intraoperatively was based on the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 4 g Octafibrin. Any administration of Octafibrin during the first 24 hours postoperatively was based on clinical judgement of need for further haemostatic support and guided by the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 2 g Octafibrin.

|  |   |
|--|---|
| <b>Arm title</b>                       | Cryoprecipitate                                 |
| Arm description: -                     |   |
| Arm type                               | Active comparator                               |
| Investigational medicinal product name | Cryoprecipitate                                 |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use                                 |

Dosage and administration details:

Cryoprecipitate was used as comparator and administered by IV injection, using an established IV route. A single unit contained a mean of approximately 400–460 mg fibrinogen. First dose of cryoprecipitate (2 pools of 5 units each) was pre-emptively administered based on clinical judgement for fibrinogen supplementation made at the 'bleeding risk assessment' time point, which took place approximately 60–90 minutes after the beginning of surgery, before 2 L of blood had been lost. Further cryoprecipitate administration intraoperatively was based on the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 2 cryoprecipitate pools of 5 units each. Any administration of cryoprecipitate during the first 24 hours postoperatively was based on clinical judgement of need for further haemostatic support and guided by the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 1 cryoprecipitate pool of 5 units.

| <b>Number of subjects in period 1</b> | Octafibirn | Cryoprecipitate |
|---------------------------------------|------------|-----------------|
| Started                               | 22         | 23              |
| Completed                             | 22         | 22              |
| Not completed                         | 0          | 1               |
| Adverse event, non-fatal              | -          | 1               |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 45            | 45    |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| median                 | 61            |       |  |
| full range (min-max)   | 34 to 76      | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 25            | 25    |  |
| Male                   | 20            | 20    |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Octafibrin                                |
| Reporting group description: -  |   |
| Reporting group title   | Cryoprecipitate                           |
| Reporting group description: -  |   |
| Subject analysis set title  | Difference in overall haemostatic success |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Test for non-inferiority between treatment groups (Octafibrin - Cryoprecipitate) |   |
| Subject analysis set title  | N (ratings)                               |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Number of ratings Octafibrin   |   |
| Subject analysis set title  | % (ratings)                               |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>% ratings Octafibrin   |   |
| Subject analysis set title  | N (ratings)                               |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Number of ratings Cryoprecipitate  |   |
| Subject analysis set title  | % (ratings)                               |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Percentage of ratings Cryoprecipitate  |   |
| Subject analysis set title  | N (total)                                 |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Total number of ratings  |   |
| Subject analysis set title  | % (total)                                 |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>Percentage of total ratings  |   |

### Primary: Frequency of the Overall Haemostatic Success Adjudicated by the IDMEAC (PP-population)

|   |   |
|---|---|
| End point title   | Frequency of the Overall Haemostatic Success Adjudicated by the IDMEAC (PP-population) <sup>[1]</sup> |
| End point description:<br>The primary efficacy endpoint was the overall haemostatic efficacy rating as assessed by the IDMEAC. Haemostatic efficacy was rated as 'excellent,' 'good,' 'moderate,' or 'none'. Ratings of 'excellent' and 'good' were considered 'haemostatic success', whereas ratings of 'moderate' and 'none' were considered 'haemostatic failure'.<br>In the primary analysis population (PP set), 100% (95% CI 83.89–100.0%) of 21 patients in the Octafibrin group and 100% (95% CI 84.56–100.0%) of the 22 patients in the cryoprecipitate group were adjudicated as having achieved 'treatment success'. |   |
| End point type  | Primary   |
| End point timeframe:<br>Overall haemostatic efficacy was determined using a predefined composite assessment algorithm based on the intraoperative and postoperative efficacy assessments and was adjudicated in a treatment-blinded manner by the IDMEAC.   |   |

Notes:

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

Justification: Due to the pathological situation (both success probabilities being equal to 1) no statistical inference on difference in proportions can be performed.

| End point values                   | Octafibirn      | Cryoprecipitate |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 21              | 22              |  |  |
| Units: Rating as Success           |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| Success Rating (N)                 | 21              | 22              |  |  |
| Success Rate (%)                   | 100             | 100             |  |  |
| 95%-Pearson Clopper interval lower | 83.89           | 84.56           |  |  |
| 95%-Pearson Clopper interval upper | 100             | 100             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Non-inferiority between treatment groups on the overall haemostatic success adjudicated by the IDMEAC (PP-population)

|                 |  |
|-----------------|--|
| End point title | Non-inferiority between treatment groups on the overall haemostatic success adjudicated by the IDMEAC (PP-population) <sup>[2]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Treatment success assessed intraoperatively and postoperatively.

Notes:

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

Justification: Due to the pathological situation (both success probabilities being equal to 1) the statistical test was performed by adding/subtracting a small epsilon (0.00001) to the subject count per treatment group. Non-inferiority margin = 0.2

| End point values                          | Difference in overall haemostatic success |  |  |  |
|---|---|--|--|--|
| Subject group type                        | Subject analysis set                      |  |  |  |
| Number of subjects analysed               | 43  |  |  |  |
| Units: Difference                         |   |  |  |  |
| number (not applicable)                   |   |  |  |  |
| Difference in overall haemostatic success | 0.0000                                    |  |  |  |
| Lower 95% confidence limit                | -0.1671                                   |  |  |  |
| Upper 95% confidence limit                | 0.1671                                    |  |  |  |
| p-value for the Farrington-Manning test   | 0.0095                                    |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Octafibrin)

|                 |  |
|-----------------|--|
| End point title | Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Octafibrin) |
|-----------------|--|

End point description:

Intraoperative haemostatic efficacy as assessed at end of surgery using an objective 4-point haemostatic efficacy scale

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

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

End point timeframe:

Intraoperative

| End point values            | N (ratings)          | % (ratings)          |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 21                   | 21                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Excellent                   | 13                   | 61.90                |  |  |
| Good                        | 7                    | 33.33                |  |  |
| Moderate                    | 1                    | 4.76                 |  |  |
| Total                       | 21                   | 100                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Cryoprecipitate)

|                 |   |
|-----------------|---|
| End point title | Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Cryoprecipitate) |
|-----------------|---|

End point description:

Intraoperative haemostatic efficacy as assessed at end of surgery using an objective 4-point haemostatic efficacy scale.

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

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

End point timeframe:

Intraoperative

| End point values            | N (ratings)          | % (ratings)          |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 22                   | 22                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Excellent                   | 12                   | 54.55                |  |  |
| Good                        | 6                    | 27.27                |  |  |
| Moderate                    | 4                    | 18.18                |  |  |
| Total                       | 22                   | 100                  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Total)

|                 |   |
|-----------------|---|
| End point title | Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Total) |
|-----------------|---|

End point description:

Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist.

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

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

End point timeframe:

Intraoperative

| End point values            | N (total)            | % (total)            |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 43                   | 43                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Excellent                   | 25                   | 58.14                |  |  |
| Good                        | 13                   | 30.23                |  |  |
| Moderate                    | 5                    | 11.63                |  |  |
| Total                       | 43                   | 100                  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Octafibrin)**

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|                 |   |
|-----------------|---|
| End point title | Postoperative haemostatic efficacy ratings assessed by haematologist (Octafibrin) |
|-----------------|---|

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed.

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

End point timeframe:

Post operative

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| End point values            | N (ratings)          | % (ratings)          |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 21                   | 21                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Exellent                    | 21                   | 100                  |  |  |
| Total                       | 21                   | 100                  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Cryoprecipitate)**

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|                 |  |
|-----------------|--|
| End point title | Postoperative haemostatic efficacy ratings assessed by haematologist (Cryoprecipitate) |
|-----------------|--|

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed

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

End point timeframe:

Post-operative

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| End point values            | N (ratings)          | % (ratings)          |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 22                   | 22                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Excellent                   | 22                   | 100                  |  |  |
| Total                       | 22                   | 100                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Total)

|                 |  |
|-----------------|--|
| End point title | Postoperative haemostatic efficacy ratings assessed by haematologist (Total) |
|-----------------|--|

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed.

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

End point timeframe:

Post-operative

| End point values            | N (total)            | % (total)            |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 43                   | 43                   |  |  |
| Units: Rating               |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Excellent                   | 43                   | 100                  |  |  |
| Total                       | 43                   | 100                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the whole study starting from the pre-operative assessment until end of the study assessment 21 days after surgery or end of hospitalization whichever ever came first.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Octafibrin |
|-----------------------|------------|

Reporting group description: -

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Cryoprecipitate |
|-----------------------|-----------------|

Reporting group description: -

| Serious adverse events                            | Octafibrin      | Cryoprecipitate  |  |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events |                 |                  |  |
| subjects affected / exposed                       | 5 / 22 (22.73%) | 13 / 23 (56.52%) |  |
| number of deaths (all causes)                     | 0               | 0                |  |
| number of deaths resulting from adverse events    | 0               | 0                |  |
| Injury, poisoning and procedural complications    |                 |                  |  |
| Gastrointestinal stoma complication               |                 |                  |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)  | 0 / 23 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Gastrointestinal anastomotic leak                 |                 |                  |  |
| subjects affected / exposed                       | 0 / 22 (0.00%)  | 1 / 23 (4.35%)   |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Pancreatic leak                                   |                 |                  |  |
| subjects affected / exposed                       | 0 / 22 (0.00%)  | 1 / 23 (4.35%)   |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Post procedural bile leak                         |                 |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular disorders                              |                |                |  |
| Haemodynamic instability                        |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Deep vein thrombosis                            |                |                |  |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 2 / 23 (8.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Angina pectoris                                 |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tachycardia                                     |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Surgical and medical procedures                 |                |                |  |
| Parenteral nutrition                            |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Constipation                                    |                |                |  |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ileus   |                |                |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                            | 0 / 22 (0.00%) | 1 / 23 (4.35%)  |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                 |  |
| Acute respiratory failure                              |                |                 |  |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 1 / 23 (4.35%)  |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                                     |                |                 |  |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 5 / 23 (21.74%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 5           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| <b>Infections and infestations</b>                     |                |                 |  |
| Pneumonia  |                |                 |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) | 2 / 23 (8.70%)  |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| Wound infection  |                |                 |  |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 1 / 23 (4.35%)  |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Octafibrin        | Cryoprecipitate   |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 22 / 22 (100.00%) | 23 / 23 (100.00%) |  |
| <b>Vascular disorders</b>                             |                   |                   |  |
| Hypertension  |                   |                   |  |
| subjects affected / exposed                           | 2 / 22 (9.09%)    | 1 / 23 (4.35%)    |  |
| occurrences (all)                                     | 2                 | 1                 |  |
| Hypotension   |                   |                   |  |
| subjects affected / exposed                           | 6 / 22 (27.27%)   | 4 / 23 (17.39%)   |  |
| occurrences (all)                                     | 6                 | 4                 |  |
| Deep vein thrombosis                                  |                   |                   |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 0 / 22 (0.00%)<br>0 | 2 / 23 (8.70%)<br>2 |  |
| General disorders and administration<br>site conditions |                     |                     |  |
| Chest discomfort  |                     |                     |  |
| subjects affected / exposed                             | 1 / 22 (4.55%)      | 2 / 23 (8.70%)      |  |
| occurrences (all)                                       | 1                   | 3                   |  |
| Oedema  |                     |                     |  |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 0 / 23 (0.00%)      |  |
| occurrences (all)                                       | 2                   | 0                   |  |
| Oedema peripheral                                       |                     |                     |  |
| subjects affected / exposed                             | 6 / 22 (27.27%)     | 3 / 23 (13.04%)     |  |
| occurrences (all)                                       | 8                   | 4                   |  |
| Pain  |                     |                     |  |
| subjects affected / exposed                             | 3 / 22 (13.64%)     | 5 / 23 (21.74%)     |  |
| occurrences (all)                                       | 4                   | 5                   |  |
| Peripheral swelling                                     |                     |                     |  |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 0 / 23 (0.00%)      |  |
| occurrences (all)                                       | 2                   | 0                   |  |
| Pyrexia   |                     |                     |  |
| subjects affected / exposed                             | 5 / 22 (22.73%)     | 8 / 23 (34.78%)     |  |
| occurrences (all)                                       | 5                   | 8                   |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |                     |  |
| Atelectasis   |                     |                     |  |
| subjects affected / exposed                             | 7 / 22 (31.82%)     | 8 / 23 (34.78%)     |  |
| occurrences (all)                                       | 7                   | 8                   |  |
| Dyspnoea  |                     |                     |  |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 3 / 23 (13.04%)     |  |
| occurrences (all)                                       | 2                   | 3                   |  |
| Lung consolidation                                      |                     |                     |  |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 3 / 23 (13.04%)     |  |
| occurrences (all)                                       | 2                   | 3                   |  |
| Non-cardiac chest pain                                  |                     |                     |  |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 1 / 23 (4.35%)      |  |
| occurrences (all)                                       | 2                   | 1                   |  |
| Oropharyngeal pain                                      |                     |                     |  |



|   |                        |                        |  |
|---|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    | 0 / 23 (0.00%)<br>0    |  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)  | 11 / 22 (50.00%)<br>11 | 11 / 23 (47.83%)<br>12 |  |
| Pleuritic pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    | 1 / 23 (4.35%)<br>1    |  |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)  | 4 / 22 (18.18%)<br>5   | 9 / 23 (39.13%)<br>9   |  |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0    | 5 / 23 (21.74%)<br>5   |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0    | 2 / 23 (8.70%)<br>2    |  |
| Psychiatric disorders<br>Hallucination<br>subjects affected / exposed<br>occurrences (all)  | 17 / 22 (77.27%)<br>17 | 17 / 23 (73.91%)<br>17 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    | 0 / 23 (0.00%)<br>0    |  |
| Panic attack<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1    | 2 / 23 (8.70%)<br>2    |  |
| Investigations<br>Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)   | 2 / 22 (9.09%)<br>2    | 2 / 23 (8.70%)<br>2    |  |
| Injury, poisoning and procedural complications<br>Gastrointestinal stoma complication<br>subjects affected / exposed<br>occurrences (all) | 2 / 22 (9.09%)<br>3    | 1 / 23 (4.35%)<br>1    |  |
| Wound complication  |                        |                        |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1    | 3 / 23 (13.04%)<br>4 |  |
| Wound dehiscence<br>subjects affected / exposed<br>occurrences (all)                                       | 3 / 22 (13.64%)<br>3   | 3 / 23 (13.04%)<br>3 |  |
| Wound secretion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1    | 2 / 23 (8.70%)<br>2  |  |
| Pancreatic leak<br>subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0    | 2 / 23 (8.70%)<br>2  |  |
| Cardiac disorders<br>Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 22 (9.09%)<br>2    | 2 / 23 (8.70%)<br>2  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 12 / 22 (54.55%)<br>13 | 8 / 23 (34.78%)<br>8 |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 22 (13.64%)<br>3   | 3 / 23 (13.04%)<br>3 |  |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    | 1 / 23 (4.35%)<br>1  |  |
| Blood and lymphatic system disorders<br>Thrombocytosis<br>subjects affected / exposed<br>occurrences (all) | 5 / 22 (22.73%)<br>5   | 8 / 23 (34.78%)<br>8 |  |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all)     | 2 / 22 (9.09%)<br>2    | 1 / 23 (4.35%)<br>1  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 22 (9.09%)<br>2    | 2 / 23 (8.70%)<br>2  |  |
| Constipation   |                        |                      |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 7 / 22 (31.82%)<br>7   | 4 / 23 (17.39%)<br>4   |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 3 / 22 (13.64%)<br>3   | 3 / 23 (13.04%)<br>3   |  |
| Ileus<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1    | 2 / 23 (8.70%)<br>2    |  |
| Intra-abdominal fluid collection<br>subjects affected / exposed<br>occurrences (all)                                 | 2 / 22 (9.09%)<br>2    | 3 / 23 (13.04%)<br>3   |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 12 / 22 (54.55%)<br>12 | 7 / 23 (30.43%)<br>7   |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 8 / 22 (36.36%)<br>8   | 10 / 23 (43.48%)<br>10 |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 22 (0.00%)<br>0    | 2 / 23 (8.70%)<br>2    |  |
| Retching<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0    | 2 / 23 (8.70%)<br>2    |  |
| Skin and subcutaneous tissue disorders<br>Subcutaneous emphysema<br>subjects affected / exposed<br>occurrences (all) | 3 / 22 (13.64%)<br>3   | 3 / 23 (13.04%)<br>3   |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)               | 3 / 22 (13.64%)<br>3   | 2 / 23 (8.70%)<br>2    |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)     | 6 / 22 (27.27%)<br>6   | 1 / 23 (4.35%)<br>1    |  |
| Infections and infestations  |                        |                        |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 22 (13.64%)<br>3 | 3 / 23 (13.04%)<br>3 |  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 22 (9.09%)<br>2  | 1 / 23 (4.35%)<br>1  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 22 (18.18%)<br>4 | 3 / 23 (13.04%)<br>3 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 2 / 22 (9.09%)<br>2  | 2 / 23 (8.70%)<br>2  |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 22 (4.55%)<br>1  | 3 / 23 (13.04%)<br>3 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 17 November 2016 | Amendment 1 : Text changed upon request of MHRA: <ul style="list-style-type: none"><li>- text regarding relevant protocol deviations has been expanded.</li><li>- text has been amended to clearly specify where in the Investigator's Brochure the Reference Safety Information and list of ADRs can be found</li><li>- text has been amended to stipulate reporting of all SAEs within 24 hours of their occurrence, as per the clarification of UK Statutory Instrument 2004 No 1031 Part 5 in the EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29</li><li>- Text has been added to define the Sponsor's responsibility in reporting all SAEs at least possibly related to the study drug as suspected unexpected serious adverse reactions (SUSARs)</li></ul> |
| 21 April 2017    | Amendment 2: <ul style="list-style-type: none"><li>-Text stating tumour stage/grade as one of the planned pre-operative baseline assessments has been deleted as pre-operative assessment of tumor grade/stage will not be performed at baseline.</li><li>- The text describing planned intraoperative assessments has been updated to include assessment of tumour stage/grade.</li><li>-The text regarding blood sampling for coagulation parameters has been expanded to provide greater clarity.</li><li>-The text defining what constitutes the end of surgery, at which point end-of-surgery assessments are to be made, has been revised to make it clearer.</li><li>- Some sentences and typos have been corrected for clearer understanding.</li></ul>                        |
| 21 November 2017 | Amendment 3:<br>An administrative interim analysis when approximately 50% of the planned patients have completed the study and adjudicated efficacy endpoint evaluation is available in these patients. has been added. This interim analysis is for administrative purposes only, no stopping rules based on statistical tests will be applied.   |
| 05 February 2018 | Amendment 4: <ul style="list-style-type: none"><li>- The planned clinical end date has been updated to 2 quarter 2018</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported