



## Clinical trial results:

**A Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of OCTAPLEX, a four-factor prothrombin complex concentrate (4F-PCC), compared to the 4F-PCC Beriplex® P/N (Kcentra), for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk.**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-002649-41   |
| Trial protocol           | DE PL ES BG RO   |
| Global end of trial date | 08 November 2021 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 December 2022 |
| First version publication date | 15 December 2022 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | LEX-209 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02740335 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Octapharma Pharmazeutika Produktionsges.m.b.H   |
| Sponsor organisation address | Oberlaaerstr. 235, Vienna, Austria, 1100  |
| Public contact               | Clinical Research & Development, Octapharma Pharmazeutika Produktionsges.m.b.H, +43 (1) 610 320 ,<br>dmitrii.matveev@octapharma.com |
| Scientific contact           | Clinical Research & Development, Octapharma Pharmazeutika Produktionsges.m.b.H, +43 (1) 610 320 ,<br>dmitrii.matveev@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                       | 08 July 2022     |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 08 November 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that the efficacy of OCTAPLEX as a reversal agent in patients under VKA therapy with the need for urgent surgery with significant bleeding risk is clinically non-inferior to Beriplex® P/N (Kcentra).

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, national regulatory requirements and FDA Code of Federal Regulations.

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 monitoring of AEs, SAEs, concomitant medication and vital status.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 07 June 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 | Romania: 51            |
| Country: Number of subjects enrolled | United States: 1       |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Georgia: 43            |
| Country: Number of subjects enrolled | Belarus: 7             |
| Country: Number of subjects enrolled | Ukraine: 94            |
| Worldwide total number of subjects   | 208                    |
| EEA total number of subjects         | 51                     |

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)                     | 78  |
| From 65 to 84 years                      | 121 |
| 85 years and over                        | 9   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients with reversal of anticoagulation due to vitamin K antagonists needing urgent surgery associated with significant bleeding risk 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                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

IP was assigned using IRT and prepared for infusion by unblinded site personnel. Investigational product was prepared and infused in a manner that blinded the investigator and other blinded site personnel to the study treatment.

### Arms

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

Arm description:

Patients received 1 Octaplex infusion intravenously

|  |  |
|--|--|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Octaplex   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solution for suspension for injection |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Investigational product was administered by IV infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min). The total volume of IP used and time of infusion was recorded. Infusion lines were to be flushed with 0.9% sodium chloride. One single infusion of IP was administered per patient

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Kcentra |
|------------------|---------|

Arm description:

Patients received 1 Beriplex® P/N (Kcentra) infusion intravenously.

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Beriplex® P/N [Kcentra],                      |
| Investigational medicinal product code |   |
| Other name                             | Kcentra                                       |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Investigational product was administered by IV infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min). The total volume of IP used and time of infusion was recorded. Infusion lines were to be flushed with 0.9% sodium chloride. One single infusion of IP was administered per patient

| <b>Number of subjects in period 1</b> | Octaplex | Kcentra |
|---------------------------------------|----------|---------|
| Started                               | 105      | 103     |
| Completed                             | 105      | 103     |

## Baseline characteristics

### Reporting groups

|   |          |
|---|----------|
| Reporting group title   | Octaplex |
| Reporting group description:  |          |
| Patients received 1 Octaplex infusion intravenously                 |          |
| Reporting group title   | Kcentra  |
| Reporting group description:  |          |
| Patients received 1 Beriplex® P/N (Kcentra) infusion intravenously. |          |

| Reporting group values                | Octaplex | Kcentra  | Total |
|---------------------------------------|----------|----------|-------|
| Number of subjects                    | 105      | 103      | 208   |
| Age categorical<br>Units: Subjects    |          |          |       |
| Age continuous<br>Units: years        |          |          |       |
| arithmetic mean                       | 65.6     | 66.8     |       |
| full range (min-max)                  | 31 to 90 | 32 to 92 | -     |
| Gender categorical<br>Units: Subjects |          |          |       |
| Female                                | 47       | 43       | 90    |
| Male                                  | 58       | 60       | 118   |

### Subject analysis sets

|   |                                  |
|---|----------------------------------|
| Subject analysis set title  | Randomized Population (RAND)     |
| Subject analysis set type   | Full analysis                    |
| Subject analysis set description:   |                                  |
| The RAND population includes all randomized patients irrespective of whether they received treatment. |                                  |
| Subject analysis set title  | Safety Analysis Population (SAF) |
| Subject analysis set type   | Safety analysis                  |
| Subject analysis set description:   |                                  |
| The SAF population includes all randomized patients who received IP.                                  |                                  |

| Reporting group values                | Randomized Population (RAND) | Safety Analysis Population (SAF) |  |
|---------------------------------------|------------------------------|----------------------------------|--|
| Number of subjects                    | 208                          | 208                              |  |
| Age categorical<br>Units: Subjects    |                              |                                  |  |
| Age continuous<br>Units: years        |                              |                                  |  |
| arithmetic mean                       | 66.2                         |                                  |  |
| full range (min-max)                  | 31 to 92                     |                                  |  |
| Gender categorical<br>Units: Subjects |                              |                                  |  |
| Female                                |                              |                                  |  |
| Male                                  |                              |                                  |  |



## End points

### End points reporting groups

|   |                                  |
|---|----------------------------------|
| Reporting group title   | Octaplex                         |
| Reporting group description:  |                                  |
| Patients received 1 Octaplex infusion intravenously   |                                  |
| Reporting group title   | Kcentra                          |
| Reporting group description:  |                                  |
| Patients received 1 Beriplex® P/N (Kcentra) infusion intravenously.                                   |                                  |
| Subject analysis set title  | Randomized Population (RAND)     |
| Subject analysis set type   | Full analysis                    |
| Subject analysis set description:   |                                  |
| The RAND population includes all randomized patients irrespective of whether they received treatment. |                                  |
| Subject analysis set title  | Safety Analysis Population (SAF) |
| Subject analysis set type   | Safety analysis                  |
| Subject analysis set description:   |                                  |
| The SAF population includes all randomized patients who received IP.                                  |                                  |

### Primary: Global Hemostatic Efficacy Observed

|   |  |
|---|--|
| End point title   | Global Hemostatic Efficacy Observed <sup>[1]</sup> |
| End point description:  |  |
| The primary efficacy variable is the hemostatic efficacy as assessed by the Independent Endpoint Adjudication Committee (IEAB). The hemostatic efficacy was assessed based on objective criteria in the categories 'excellent', 'good', 'moderate' or 'none'. Ratings of 'excellent' and 'good' are to be considered as 'effective' hemostasis, while a rating of 'moderate' and 'none' are to be considered as 'ineffective' hemostasis. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| At end of the surgery   |  |
| 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: No statistical analysis for this endpoint.   |  |

| End point values            | Octaplex        | Kcentra         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 105             | 103             |  |  |
| Units: number of patients   |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Excellent                   | 41              | 50              |  |  |
| Good                        | 58              | 47              |  |  |
| Moderate                    | 6               | 6               |  |  |
| None                        | 0               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Non-inferiority Proportion Difference Octaplex vs Kcentra



|   |   |
|---|---|
| End point title   | Non-inferiority Proportion Difference Octaplex vs Kcentra |
| End point description:  |   |
| The dichotomous 'hemostatic success' variable was used in the analyses to demonstrate that treatment with Octaplex was clinically not inferior to treatment with Beriplex® P/N (Kcentra) with respect to hemostatic success. Effective hemostasis includes Excellent and Good ratings, while Ineffective hemostasis includes Moderate and None ratings from Global hemostatic efficacy observed by IEAB. Imputation for Ineffective was performed for missing rating or additional coagulation after initial IP infusion as None. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| At end of the surgery   |   |

| End point values            | Octaplex        | Kcentra         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 105             | 103             |  |  |
| Units: number of patients   |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Effective                   | 99              | 97              |  |  |
| Ineffective                 | 6               | 6               |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Non-inferiority Difference Octaplex vs Kcentra.... |
| Comparison groups                       | Octaplex v Kcentra                                 |
| Number of subjects included in analysis | 208  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | non-inferiority                                    |
| P-value                                 | < 0.001  |
| Method                                  | Farrington's and Manning's test                    |
| Parameter estimate                      | Proportion difference                              |
| Point estimate                          | 0.001  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.08  |
| upper limit                             | 0.082  |

### Secondary: Patients with an INR value of less or equal to 1.5 at 30 (± 15) minutes after the end of infusion

|  |   |
|--|---|
| End point title  | Patients with an INR value of less or equal to 1.5 at 30 (± 15) minutes after the end of infusion |
| End point description:   |   |
| Proportion of patients with an INR value of less or equal to 1.5 at 30 (± 15) minutes after the end of infusion. |   |
| End point type   | Secondary   |

End point timeframe:

30 ( $\pm$  15) minutes after the end of infusion.

| End point values            | Octaplex        | Kcentra         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 105             | 103             |  |  |
| Units: patients             |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| <= 1.5                      | 82              | 74              |  |  |
| > 1.5                       | 23              | 29              |  |  |
| Missing                     | 0               | 0               |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Proportion difference Octaplex VS Kcentra |
| Comparison groups                       | Octaplex v Kcentra                        |
| Number of subjects included in analysis | 208                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[2]</sup>                      |
| Parameter estimate                      | Proportion difference                     |
| Point estimate                          | 0.063                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.056                                    |
| upper limit                             | 0.181                                     |

Notes:

[2] - Farrington's and Manning's test for difference in proportions was performed.

### Secondary: Change in Coagulation Factor FII Level

|                        |   |
|------------------------|---|
| End point title        | Change in Coagulation Factor FII Level  |
| End point description: | Change in coagulation factor FII level from baseline to 30 ( $\pm$ 15) minutes after the end of infusion. |
| End point type         | Secondary   |
| End point timeframe:   | 30 ( $\pm$ 15) minutes after the end of infusion.   |

| End point values                     | Octaplex        | Kcentra            |  |  |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type                   | Reporting group | Reporting group    |  |  |
| Number of subjects analysed          | 104             | 100 <sup>[3]</sup> |  |  |
| Units: FII activity (%)              |                 |                    |  |  |
| arithmetic mean (standard deviation) |                 |                    |  |  |
| Mean baseline                        | 33.7 (± 19.8)   | 34.4 (± 19.6)      |  |  |
| Mean change from baseline            | 56.5 (± 29.4)   | 55.6 (± 28.7)      |  |  |

Notes:

[3] - Baseline: 101 patients

Change from Baseline: 100 patients

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title              | Median Difference Octaplex vs Kcentra |
| Comparison groups                       | Octaplex v Kcentra                    |
| Number of subjects included in analysis | 204                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other                                 |
| Parameter estimate                      | Median difference                     |
| Point estimate                          | 1                                     |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -7                                    |
| upper limit                             | 9                                     |

## Secondary: Change in Coagulation Factor FVII Level

|   |   |
|---|---|
| End point title   | Change in Coagulation Factor FVII Level |
| End point description:  |   |
| Change in coagulation factor FVII level from baseline to 30 (± 15) minutes after the end of infusion. |   |
| End point type  | Secondary                               |
| End point timeframe:  |   |
| 30 (± 15) minutes after the end of infusion.  |   |

| End point values                     | Octaplex        | Kcentra         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 105             | 102             |  |  |
| Units: FVII activity (%)             |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Mean baseline                        | 27.6 (± 25.1)   | 27.3 (± 23.1)   |  |  |
| Mean change from baseline            | 40.9 (± 32.8)   | 32.8 (± 34.4)   |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Median Difference Octaplex vs Kcentra |
| Comparison groups                       | Kcentra v Octaplex                    |
| Number of subjects included in analysis | 207                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other                                 |
| Parameter estimate                      | Median difference                     |
| Point estimate                          | 8                                     |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 2                                     |
| upper limit                             | 15                                    |

### Secondary: Change in Coagulation Factor FIX Level

|                        |   |
|------------------------|---|
| End point title        | Change in Coagulation Factor FIX Level  |
| End point description: | Change in coagulation factor FIX level from baseline to 30 ( $\pm$ 15) minutes after the end of infusion. |
| End point type         | Secondary   |
| End point timeframe:   | 30 ( $\pm$ 15) minutes after the end of infusion.   |

| End point values                     | Octaplex           | Kcentra            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 105                | 102                |  |  |
| Units: FIX activity (%)              |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Mean baseline                        | 53.0 ( $\pm$ 32.2) | 53.6 ( $\pm$ 31.4) |  |  |
| Mean change from baseline            | 36.9 ( $\pm$ 37.6) | 36.5 ( $\pm$ 33.2) |  |  |

### Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Median Difference Octaplex vs Kcentra |
| Comparison groups                       | Octaplex v Kcentra                    |
| Number of subjects included in analysis | 207                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other                                 |
| Parameter estimate                      | Proportion difference                 |
| Point estimate                          | 0                                     |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -7                                    |
| upper limit                             | 8                                     |

## Secondary: Change in Coagulation Factor FX Level

|  |                                       |
|--|---------------------------------------|
| End point title  | Change in Coagulation Factor FX Level |
| End point description:<br>Change in coagulation factor FX level from baseline to 30 ( $\pm$ 15) minutes after the end of infusion. |                                       |
| End point type   | Secondary                             |
| End point timeframe:<br>30 ( $\pm$ 15) minutes after the end of infusion.  |                                       |

| End point values                     | Octaplex           | Kcentra            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 103                | 99 <sup>[4]</sup>  |  |  |
| Units: FX activity (%)               |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Mean baseline                        | 24.4 ( $\pm$ 17.6) | 24.0 ( $\pm$ 18.6) |  |  |
| Mean change from baseline            | 56.0 ( $\pm$ 29.8) | 69.0 ( $\pm$ 32.3) |  |  |

Notes:

[4] - Baseline: 100 patients

Change from Baseline: 99 patients

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title              | Median Difference Octaplex vs Kcentra |
| Comparison groups                       | Octaplex v Kcentra                    |
| Number of subjects included in analysis | 202                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other                                 |
| Parameter estimate                      | Median difference                     |
| Point estimate                          | -13                                   |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -21                                   |
| upper limit                             | 4                                     |

## Secondary: Red Blood Cells Received During Surgery

|   |   |
|---|---|
| End point title   | Red Blood Cells Received During Surgery |
| End point description:<br>Proportion of patients receiving red blood cells. |   |
| End point type  | Secondary                               |
| End point timeframe:<br>during surgery                                      |   |

| <b>End point values</b>     | Octaplex        | Kcentra         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 105             | 103             |  |  |
| Units: patients             |                 |                 |  |  |
| number (not applicable)     | 4               | 3               |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Proportion difference Octaplex VS Kcentra |
|---|---|
| Comparison groups                       | Octaplex v Kcentra                        |
| Number of subjects included in analysis | 208                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other                                     |
| Parameter estimate                      | Proportion difference                     |
| Point estimate                          | 0.009                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.068                                    |
| upper limit                             | 0.086                                     |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the whole study from baseline up to day 45 (follow up visit)

Adverse event reporting additional description:

AEs were to be followed-up until Day 4. SAEs were to be followed-up until Day 45. If TEEs were suspected at any time during the study, appropriate examinations according to local standards were performed

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Octaplex |
|-----------------------|----------|

Reporting group description:

Patients received 1 Octaplex infusion intravenously

|                       |         |
|-----------------------|---------|
| Reporting group title | Kcentra |
|-----------------------|---------|

Reporting group description:

Patients received 1 Kcentra infusions intravenously

| Serious adverse events  | Octaplex          | Kcentra         |  |
|---|-------------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                   |                 |  |
| subjects affected / exposed   | 13 / 105 (12.38%) | 6 / 103 (5.83%) |  |
| number of deaths (all causes)                                       | 5                 | 1               |  |
| number of deaths resulting from adverse events                      | 0                 | 0               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                 |  |
| Ovarian cancer stage IV   |                   |                 |  |
| subjects affected / exposed   | 0 / 105 (0.00%)   | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0           |  |
| Injury, poisoning and procedural complications                      |                   |                 |  |
| Anastomotic haemorrhage   |                   |                 |  |
| subjects affected / exposed   | 1 / 105 (0.95%)   | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0           |  |
| Failure to anastomose   |                   |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint dislocation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound complication                |                 |                 |  |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Shock   |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                             |                 |                 |  |
| Cerebral infarction                                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders                 |                 |                 |  |
| Anaemia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Haemorrhagic Anaemia                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| Gastritis erosive                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mesenteric haematoma                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proctitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis haemorrhagic                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| 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 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Soft tissue haemorrhage<br>subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to<br>treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>                     |                 |                 |  |
| Orchitis   |                 |                 |  |
| subjects affected / exposed                            | 1 / 105 (0.95%) | 0 / 103 (0.00%) |  |
| occurrences causally related to<br>treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           |  |
| Pneumonia  |                 |                 |  |
| subjects affected / exposed                            | 0 / 105 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                        | Octaplex          | Kcentra           |  |
|--|-------------------|-------------------|--|
| Total subjects affected by non-serious<br>adverse events |                   |                   |  |
| subjects affected / exposed                              | 85 / 105 (80.95%) | 80 / 103 (77.67%) |  |
| Investigations   |                   |                   |  |
| Blood pressure increased                                 |                   |                   |  |
| subjects affected / exposed                              | 0 / 105 (0.00%)   | 5 / 103 (4.85%)   |  |
| occurrences (all)  | 0                 | 5                 |  |
| Body temperature increased                               |                   |                   |  |
| subjects affected / exposed                              | 0 / 105 (0.00%)   | 4 / 103 (3.88%)   |  |
| occurrences (all)  | 0                 | 4                 |  |
| Injury, poisoning and procedural<br>complications        |                   |                   |  |
| Procedural pain  |                   |                   |  |
| subjects affected / exposed                              | 50 / 105 (47.62%) | 50 / 103 (48.54%) |  |
| occurrences (all)  | 51                | 50                |  |
| Postoperative wound complication                         |                   |                   |  |
| subjects affected / exposed                              | 15 / 105 (14.29%) | 14 / 103 (13.59%) |  |
| occurrences (all)  | 15                | 15                |  |
| Procedural vomiting                                      |                   |                   |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 4 / 105 (3.81%)<br>4    | 0 / 103 (0.00%)<br>0    |  |
| Suture related complication<br>subjects affected / exposed<br>occurrences (all)   | 2 / 105 (1.90%)<br>2    | 4 / 103 (3.88%)<br>4    |  |
| Vascular disorders<br>Hypotension<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 105 (0.00%)<br>0    | 3 / 103 (2.91%)<br>4    |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 105 (5.71%)<br>6    | 6 / 103 (5.83%)<br>6    |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 13 / 105 (12.38%)<br>13 | 18 / 103 (17.48%)<br>22 |  |
| Catheter site related reaction<br>subjects affected / exposed<br>occurrences (all)                                      | 4 / 105 (3.81%)<br>5    | 2 / 103 (1.94%)<br>2    |  |
| Hyperthermia<br>subjects affected / exposed<br>occurrences (all)  | 3 / 105 (2.86%)<br>3    | 2 / 103 (1.94%)<br>2    |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 105 (0.95%)<br>1    | 3 / 103 (2.91%)<br>3    |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 105 (2.86%)<br>3    | 5 / 103 (4.85%)<br>5    |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)  | 2 / 105 (1.90%)<br>2    | 3 / 103 (2.91%)<br>3    |  |
| Dyschezia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 105 (0.95%)<br>1    | 3 / 103 (2.91%)<br>3    |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 105 (0.00%)<br>0 | 3 / 103 (2.91%)<br>3 |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)   | 5 / 105 (4.76%)<br>5 | 2 / 103 (1.94%)<br>2 |  |
| Infections and infestations<br>Pneumonia<br>subjects affected / exposed<br>occurrences (all) | 1 / 105 (0.95%)<br>1 | 2 / 103 (1.94%)<br>2 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 21 October 2016 | Protocol version 3.0, 21.10.2016:<br>-Additional changes in response to the FDA advice dated October 6, 2016.<br>-ICF revised to align with revised protocol.<br>-Safety section updated to cover post marketing experience of Octaplex use, align with IB ed.10 |
| 19 January 2018 | Protocol version 4.0, 19.01.2018<br>- Amendment #1 dated 19-Jan-2018 incorporated: Changes to clarify the text based on the investigators questions and feedback (clarification of ex/in criteria, admin. changes).  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date |
|------------------|--|--------------|
| 08 November 2021 | The study was conducted in 2 stages, with one un-blinded interim analysis after enrollment of 50% of the planned sample size, to allow for an early stopping of the study for demonstrated non-inferiority of OCTAPLEX or to allow for an early stopping due to futility to achieve this. As study success was claimed on the interim results enrollment of additional patients was prematurely discontinued (as agreed by the FDA on 22-Feb-2022), and this report of the final analysis was prepared. All patients enrolled until a decision to stop the study was made were observed until the end of the follow-up period. The interim analysis was performed by a statistical team which was independent from the study team. The decision to prematurely terminate the study was made in consultation with the relevant authorities. | -            |

Notes:

### Limitations and caveats

None reported