



## Clinical trial results:

**A randomized, active-controlled, multicenter, phase III study investigating efficacy and safety of intra-operative use of BT524 (human fibrinogen concentrate) in subjects undergoing major spinal or abdominal surgery (AdFlrst).**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-001163-20   |
| Trial protocol           | DE BE ES CZ GB   |
| Global end of trial date | 21 November 2023 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 29 November 2024 |
| First version publication date | 29 November 2024 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | Study No. 995 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03444324 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Biotest AG   |
| Sponsor organisation address | Landsteinerstr. 5, Dreieich, Germany, 63303                                |
| Public contact               | Corporate Clinical Research, Biotest AG, 0049 61038016395, 995@biotest.com |
| Scientific contact           | Corporate Clinical Research, Biotest AG, 0049 61038016395, 995@biotest.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                       | 06 February 2024 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 21 November 2023 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 November 2023 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this phase III trial was to demonstrate the efficacy of fibrinogen concentrate (BT524) as a complementary therapy for the management of uncontrolled severe hemorrhage in subjects with acquired hypofibrinogenemia undergoing elective major spinal or abdominal surgery. The primary objective of this study was to demonstrate that BT524 is non-inferior, that means not worse than fresh frozen plasma (FFP)/cryoprecipitate with a non-inferiority margin of 150 mL in reducing intra-operative blood loss by intravenous (IV) administration in subjects with acquired hypofibrinogenemia undergoing elective major spinal or abdominal surgery. If therapeutical equivalence (non-inferiority) had been demonstrated, therapeutic superiority of BT524 compared with FFP/cryoprecipitate was also to be assessed.

Protection of trial subjects:

The trial was conducted in accordance with the ICH-GCP guidelines, the most recent version of the Declaration of Helsinki, with local regulatory requirements, and in accordance with standard operating procedures for clinical research at Biotest AG and the contract research organization. A Data Safety Monitoring Board (DSMB) independently reviewed and assessed the unblinded safety data throughout the entire trial at regular intervals. The DSMB members were unblinded during the evaluation periods and were provided with the following information: reports of Serious Adverse Events and Adverse Events, data on markers of coagulation and coagulation factors, clinical laboratory assessments of hematology, clinical chemistry and urinalysis, and vital signs. The DSMB were provided with data covering the screening visit, the day of surgery plus 4 additional follow-up visits and evaluated the subjects' risks at formal DSMB meetings with regards to the relevant parameters and outcome criteria. In addition, subject's data from the closing visit were also be evaluated if data already available at the time of the DSMB meeting. The DSMB members could propose to stop the trial at any time after a scheduled or unscheduled meeting in case of major safety concerns related to trial treatment.

Background therapy:

None

Evidence for comparator:

FFP was used as active comparator to BT524 in subjects undergoing major spinal surgery. FFP is the standard of care in many European countries for replacement of coagulation factors during major bleeding in clinical settings such as surgery and trauma. Standard FFP contains 2-5 mg fibrinogen per mL.

Cryoprecipitate was used as active comparator to BT524 in subjects undergoing cytoreductive PMP surgery at one site in the UK. Cryoprecipitate is produced in the UK, USA, Canada, Australia, and New Zealand, where it is mainly used as a concentrated source of fibrinogen for treatment of acquired hypofibrinogenemia. Cryoprecipitate is available as single units or as pools of five. A single unit contains a mean of approximately 400 to 460 mg fibrinogen.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 03 April 2018 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Belgium: 1          |
| Country: Number of subjects enrolled | Switzerland: 24     |
| Country: Number of subjects enrolled | Poland: 1           |
| Country: Number of subjects enrolled | Spain: 53           |
| Country: Number of subjects enrolled | United Kingdom: 109 |
| Country: Number of subjects enrolled | Czechia: 67         |
| Country: Number of subjects enrolled | Germany: 84         |
| Worldwide total number of subjects   | 339                 |
| EEA total number of subjects         | 206                 |

Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 167 |
| From 65 to 84 years                       | 169 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was based on the surgeons' clinical assessments during physical examinations and personal consultations prior to spinal or abdominal surgery (Day -42 to Day -1), which were conducted at the respective hospitals where surgeries were scheduled to take place.

### Pre-assignment

Screening details:

Eligible subjects were those scheduled for elective major spinal or abdominal surgery with an expected major blood loss. While the type of spinal surgery was not restricted, the abdominal surgery was limited to cytoreductive surgery for pseudomyxoma peritonei (PMP). Screening occurred during a dedicated visit within 42 days before surgery.

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 339 |
| Number of subjects completed | 222 |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Adverse event, non-fatal: 2                      |
| Reason: Number of subjects | Consent withdrawn by subject: 10                 |
| Reason: Number of subjects | Physician decision: 21                           |
| Reason: Number of subjects | Eligibility criteria prior surgery not met: 11   |
| Reason: Number of subjects | Intra-operative eligibility criteria not met: 69 |
| Reason: Number of subjects | Technical reason: 3                              |
| Reason: Number of subjects | Other: 1   |

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Intra-operative, from decision to treat (overall period) |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                                  |
| Blinding used                | Single blind   |
| Roles blinded                | Subject  |

Blinding implementation details:

This trial was partially blinded; surgeon, surgical staff, and subjects were blinded to treatment allocation throughout the entire surgery. The anesthesiologist who administered the IMP was not blinded to treatment allocation because of the inherent characteristics of the IMPs (BT524, FFP, and cryoprecipitate).

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| Arm title                    | BT524 |

Arm description:

BT524 is a lyophilized, heat-treated, virus and prion safe human fibrinogen concentrate manufactured from human plasma used as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenemia.

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

|  |  |
|--|--|
| Investigational medicinal product name | BT524                                      |
| Investigational medicinal product code | BT524                                      |
| Other name                             | Human fibrinogen concentrate               |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Infusion , Intravenous use                 |

**Dosage and administration details:**

For subjects who underwent spinal surgery, BT524 dose was calculated based on the subject's body weight (BW) and the functional fibrinogen levels (FIBTEM A10) measured by ROTEM thromboelastometry with the aim of restoring the individual baseline FIBTEM A10 value, using a given formula. First dose was at least 2g and the maximum dose of fibrinogen concentrate during surgery should not exceed 8g.

For subjects who underwent cytoreductive PMP surgery, the dose of BT524 infused was a fixed dose of 4g with the aim of restoring the fibrinogen plasma level per guidelines. The first BT524 dose was administered pre-emptively. Subjects randomized to the BT524 group received 4g BT524 each time fibrinogen supplementation was ordered.

BT524 was administered intravenously.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | FFP/Cryo |
|------------------|----------|

**Arm description:**

Conventional replacement therapy with fresh frozen plasma or cryoprecipitate, used during surgery to supplement fibrinogen in case of bleeding.

|  |                            |
|--|----------------------------|
| Arm type                               | Active comparator          |
| Investigational medicinal product name | Fresh Frozen Plasma        |
| Investigational medicinal product code | FFP                        |
| Other name                             |                            |
| Pharmaceutical forms                   | Sterile concentrate        |
| Routes of administration               | Infusion , Intravenous use |

**Dosage and administration details:**

Dosage was based on local standards and depended on the extent of bleeding and the subject's clinical condition. The recommended dose of FFP was 15 mL per kg body weight (BW).

Subsequent intra-operative infusions were given as required. FFP was administered intravenously.

|  |                            |
|--|----------------------------|
| Investigational medicinal product name | Cryoprecipitate            |
| Investigational medicinal product code | Cryo                       |
| Other name                             |                            |
| Pharmaceutical forms                   | Sterile concentrate        |
| Routes of administration               | Infusion , Intravenous use |

**Dosage and administration details:**

The therapeutic cryoprecipitate dose was two pools, each pool consisting of 5 units (10 units, dose-equivalent to 4g fibrinogen concentrate). The first cryoprecipitate dose was administered pre-emptively. Subjects randomized to the cryoprecipitate group received two pools cryoprecipitate each time fibrinogen supplementation was ordered. Cryo was administered intravenously.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | BT524 | FFP/Cryo |
|---|-------|----------|
| Started   | 110   | 112      |
| Randomization                                       | 110   | 112      |
| Completed   | 105   | 106      |
| Not completed                                       | 5     | 6        |
| Consent withdrawn by subject                        | -     | 1        |
| Other   | -     | 1        |
| Lack of Study Compliance                            | 1     | 1        |
| Lost to follow-up                                   | 4     | 2        |

|                    |   |   |
|--------------------|---|---|
| Protocol deviation | - | 1 |
|--------------------|---|---|

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The group 'All subjects enrolled' includes all subjects who provided informed consent during the screening visit (n=339). Of these, n=117 were screening failures. Intraoperatively, at the time of the 'decision to treat,' n=222 subjects were deemed eligible and were randomised. Baseline data were analyzed only for this group of randomised subjects. The intraoperative period, starting from the decision to treat, is considered the baseline period.

## Baseline characteristics

### Reporting groups

|  |          |
|--|----------|
| Reporting group title  | BT524    |
| Reporting group description:<br>BT524 is a lyophilized, heat-treated, virus and prion safe human fibrinogen concentrate manufactured from human plasma used as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenemia. |          |
| Reporting group title  | FFP/Cryo |
| Reporting group description:<br>Conventional replacement therapy with fresh frozen plasma or cryoprecipitate, used during surgery to supplement fibrinogen in case of bleeding.  |          |

| Reporting group values                             | BT524   | FFP/Cryo | Total |
|--|---------|----------|-------|
| Number of subjects                                 | 110     | 112      | 222   |
| Age categorical                                    |         |          |       |
| Units: Subjects                                    |         |          |       |
| In utero   | 0       | 0        | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0        | 0     |
| Newborns (0-27 days)                               | 0       | 0        | 0     |
| Infants and toddlers (28 days-23 months)           | 0       | 0        | 0     |
| Children (2-11 years)                              | 0       | 0        | 0     |
| Adolescents (12-17 years)                          | 0       | 0        | 0     |
| Adults (18-64 years)                               | 62      | 58       | 120   |
| From 65-84 years                                   | 48      | 54       | 102   |
| 85 years and over                                  | 0       | 0        | 0     |
| Age continuous                                     |         |          |       |
| Adults aged ≥ 18                                   |         |          |       |
| Units: years                                       |         |          |       |
| arithmetic mean                                    | 61.2    | 60.8     |       |
| standard deviation                                 | ± 12.52 | ± 14.07  | -     |
| Gender categorical                                 |         |          |       |
| Units: Subjects                                    |         |          |       |
| Female   | 67      | 64       | 131   |
| Male   | 43      | 48       | 91    |

### Subject analysis sets

|  |                            |
|--|----------------------------|
| Subject analysis set title   | Safety Set                 |
| Subject analysis set type  | Safety analysis            |
| Subject analysis set description:<br>The Safety Analysis Set (SAF) comprises all subjects who have received at least one dose of IMP.                              |                            |
| Subject analysis set title   | Full Analysis Set          |
| Subject analysis set type  | Full analysis              |
| Subject analysis set description:<br>All randomized subjects receiving IMP post randomization and with data collected post randomization were included in the FAS. |                            |
| Subject analysis set title   | Modified Full Analysis Set |
| Subject analysis set type  | Sub-group analysis         |

Subject analysis set description:

All randomized subjects who met the following conditions were included in the Modified Full Analysis Set (mFAS): Subjects who received at least one dose of IMP prior to the 'end of surgery' and have at least one postdose efficacy assessment. This included all subjects whose IMP infusion started prior to the end of surgery, irrespective of the amount of IMP infused.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Per-Protocol Set |
| Subject analysis set type  | Per protocol     |

Subject analysis set description:

The Per-Protocol Set is a subset of FAS and included all subjects who were compliant with the clinical trial protocol without any major protocol deviations thought to have the potential to impact the results of the efficacy analysis, e.g., no treatment with IMP, incomplete treatment with IMP (administration of the first IMP dose was not completed if the end of the first IMP administration was after the end of surgery), treatment with IMP after the 'end of surgery', no postdose efficacy assessment for the primary endpoint.

| Reporting group values                             | Safety Set | Full Analysis Set | Modified Full Analysis Set |
|--|------------|-------------------|----------------------------|
| Number of subjects                                 | 222        | 222               | 211                        |
| Age categorical                                    |            |                   |                            |
| Units: Subjects                                    |            |                   |                            |
| In utero   | 0          | 0                 | 0                          |
| Preterm newborn infants (gestational age < 37 wks) | 0          | 0                 | 0                          |
| Newborns (0-27 days)                               | 0          | 0                 | 0                          |
| Infants and toddlers (28 days-23 months)           | 0          | 0                 | 0                          |
| Children (2-11 years)                              | 0          | 0                 | 0                          |
| Adolescents (12-17 years)                          | 0          | 0                 | 0                          |
| Adults (18-64 years)                               | 120        | 120               | 114                        |
| From 65-84 years                                   | 102        | 102               | 97                         |
| 85 years and over                                  | 0          | 0                 | 0                          |
| Age continuous                                     |            |                   |                            |
| Adults aged ≥ 18                                   |            |                   |                            |
| Units: years                                       |            |                   |                            |
| arithmetic mean                                    | 61.0       | 61.0              | 61.2                       |
| standard deviation                                 | ± 13.29    | ± 13.29           | ± 12.82                    |
| Gender categorical                                 |            |                   |                            |
| Units: Subjects                                    |            |                   |                            |
| Female   | 131        | 131               | 121                        |
| Male   | 91         | 91                | 90                         |

| Reporting group values                             | Per-Protocol Set |  |  |
|--|------------------|--|--|
| Number of subjects                                 | 201              |  |  |
| Age categorical                                    |                  |  |  |
| Units: Subjects                                    |                  |  |  |
| In utero   | 0                |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 110              |  |  |
| From 65-84 years                                   | 91               |  |  |
| 85 years and over                                  | 0                |  |  |



|                       |             |  |  |
|-----------------------|-------------|--|--|
| Age continuous        |             |  |  |
| Adults aged $\geq 18$ |             |  |  |
| Units: years          |             |  |  |
| arithmetic mean       | 60.9        |  |  |
| standard deviation    | $\pm 12.95$ |  |  |
| Gender categorical    |             |  |  |
| Units: Subjects       |             |  |  |
| Female                | 115         |  |  |
| Male                  | 86          |  |  |

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## End points

### End points reporting groups

|  |                            |
|--|----------------------------|
| Reporting group title  | BT524                      |
| Reporting group description:<br>BT524 is a lyophilized, heat-treated, virus and prion safe human fibrinogen concentrate manufactured from human plasma used as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenemia.   |                            |
| Reporting group title  | FFP/Cryo                   |
| Reporting group description:<br>Conventional replacement therapy with fresh frozen plasma or cryoprecipitate, used during surgery to supplement fibrinogen in case of bleeding.  |                            |
| Subject analysis set title   | Safety Set                 |
| Subject analysis set type  | Safety analysis            |
| Subject analysis set description:<br>The Safety Analysis Set (SAF) comprises all subjects who have received at least one dose of IMP.  |                            |
| Subject analysis set title   | Full Analysis Set          |
| Subject analysis set type  | Full analysis              |
| Subject analysis set description:<br>All randomized subjects receiving IMP post randomization and with data collected post randomization were included in the FAS.   |                            |
| Subject analysis set title   | Modified Full Analysis Set |
| Subject analysis set type  | Sub-group analysis         |
| Subject analysis set description:<br>All randomized subjects who met the following conditions were included in the Modified Full Analysis Set (mFAS): Subjects who received at least one dose of IMP prior to the 'end of surgery' and have at least one postdose efficacy assessment. This included all subjects whose IMP infusion started prior to the end of surgery, irrespective of the amount of IMP infused.   |                            |
| Subject analysis set title   | Per-Protocol Set           |
| Subject analysis set type  | Per protocol               |
| Subject analysis set description:<br>The Per-Protocol Set is a subset of FAS and included all subjects who were compliant with the clinical trial protocol without any major protocol deviations thought to have the potential to impact the results of the efficacy analysis, e.g., no treatment with IMP, incomplete treatment with IMP (administration of the first IMP dose was not completed if the end of the first IMP administration was after the end of surgery), treatment with IMP after the 'end of surgery', no postdose efficacy assessment for the primary endpoint. |                            |

### Primary: Intra-operative blood loss

|   |                            |
|---|----------------------------|
| End point title   | Intra-operative blood loss |
| End point description:<br>Intra-operative blood loss after decision to treat the subject with IMP until the end of surgery as measured by amount of blood from the blood suction unit and amount of blood from swabs, surgical cloths and compresses. |                            |
| End point type  | Primary                    |
| End point timeframe:<br>After decision to treat the subject with IMP until the end of surgery.  |                            |

| End point values                             | BT524                           | FFP/Cryo                        |  |  |
|--|---------------------------------|---------------------------------|--|--|
| Subject group type                           | Reporting group                 | Reporting group                 |  |  |
| Number of subjects analysed                  | 103 <sup>[1]</sup>              | 98 <sup>[2]</sup>               |  |  |
| Units: mL                                    |                                 |                                 |  |  |
| least squares mean (confidence interval 95%) | 1380.70<br>(1187.09 to 1574.31) | 1660.13<br>(1460.65 to 1895.61) |  |  |

Notes:

[1] - Per-Protocol Set

[2] - Per-Protocol Set

## Statistical analyses

| Statistical analysis title  | Primary Non-inferiority Analysis |
|---|----------------------------------|
| Statistical analysis description:   |                                  |
| Primary Non-inferiority Analysis of Intra-operative Blood Loss after Decision to Treat with IMP until the End of Surgery - Per-protocol Set |                                  |
| Comparison groups   | FFP/Cryo v BT524                 |
| Number of subjects included in analysis   | 201                              |
| Analysis specification  | Pre-specified                    |
| Analysis type   | non-inferiority <sup>[3]</sup>   |
| P-value   | < 0.001 <sup>[4]</sup>           |
| Method  | Van Elteren test                 |
| Parameter estimate  | Difference in LSM                |
| Point estimate  | -279.43                          |
| Confidence interval   |                                  |
| level   | 95 %                             |
| sides   | 2-sided                          |
| lower limit   | -552.38                          |
| upper limit   | -6.48                            |

Notes:

[3] - The primary efficacy analysis of this endpoint was to test non-inferiority in the Per-protocol Set (PPS). The final analysis was performed using a two-way analysis of variance (ANOVA). Non-inferiority was to be demonstrated if the upper confidence limit of the two-sided 95 % confidence interval (CI) for the difference in the least squares mean (LSM) was less than the non-inferiority margin (150 mL).

[4] - p-value from Van Elteren test, stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL).

## Secondary: Subjects with successful correction of fibrinogen level

| End point title  | Subjects with successful correction of fibrinogen level |
|--|---|
| End point description:   |   |
| The proportion (%) of subjects with a successful correction of fibrinogen level (by FIBTEM A10) 15 minutes after start of first IMP administration will be compared between the treatment arms using a Cochran-Mantel-Haenszel (CMH) approach stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL). |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| 15 minutes after the start of the first IMP administration   |   |

| End point values            | BT524              | FFP/Cryo           |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 104 <sup>[5]</sup> | 102 <sup>[6]</sup> |  |  |
| Units: Number of subjects   | 59                 | 19                 |  |  |

Notes:

[5] - mFAS

[6] - mFAS

## Statistical analyses

| Statistical analysis title  | Correction of Fibrinogen Level |
|---|--------------------------------|
| Statistical analysis description:   |                                |
| The proportion (%) of subjects with a successful correction of fibrinogen level (by FIBTEM A10) 15 minutes after start of first IMP administration will be compared between the treatment arms using a Cochran-Mantel-Haenszel (CMH) approach stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL). The number and percentage of subjects with a successful correction of fibrinogen level 15 minutes after start of first IMP administration will be presented for both treatment arms. |                                |
| Comparison groups   | BT524 v FFP/Cryo               |
| Number of subjects included in analysis   | 206                            |
| Analysis specification  | Pre-specified                  |
| Analysis type   | other                          |
| P-value   | < 0.001 <sup>[7]</sup>         |
| Method  | Cochran-Mantel-Haenszel        |
| Parameter estimate  | Difference in response rate    |
| Point estimate  | 38.1                           |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | 26                             |
| upper limit   | 50.3                           |

Notes:

[7] - P-value is from a Cochran-Mantel-Haenszel model stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL).

## Secondary: Time to first successful correction of fibrinogen level

| End point title   | Time to first successful correction of fibrinogen level |
|---|---|
| End point description:  |   |
| The 4 categories were compared between the two treatment arms using a Chi-square test. For the above Chi-square test, the number and percentage of subjects in each category were presented for each treatment arm, together with an overall p-value for the difference between the two treatment arms. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Within 15 minutes after IMP start, >15 and ≤ 90 minutes after IMP start, >90 minutes after IMP start, unsuccessful correction.  |   |

| End point values                     | BT524              | FFP/Cryo           |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 107 <sup>[8]</sup> | 104 <sup>[9]</sup> |  |  |
| Units: Number of subjects            |                    |                    |  |  |
| ≤15 minutes after IMP start          | 59                 | 19                 |  |  |
| >15 and ≤ 90 minutes after IMP start | 17                 | 11                 |  |  |

|                             |    |    |  |  |
|-----------------------------|----|----|--|--|
| >90 minutes after IMP start | 11 | 16 |  |  |
| Unsuccessful correction     | 20 | 58 |  |  |

Notes:

[8] - mFAS

[9] - mFAS

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Time to first Correction of Fibrinogen level |
|-----------------------------------|--|

Statistical analysis description:

The two treatment arms were compared using a Chi-Square test.

|   |                  |
|---|------------------|
| Comparison groups                       | BT524 v FFP/Cryo |
| Number of subjects included in analysis | 211              |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | other            |
| P-value                                 | < 0.001          |
| Method                                  | Chi-squared      |

## Secondary: Amount of transfusion products

|                 |                                |
|-----------------|--------------------------------|
| End point title | Amount of transfusion products |
|-----------------|--------------------------------|

End point description:

Total amount (volume) of transfusion products (allogeneic blood products) or autologous blood transfusion infused after start of first IMP administration until end of surgery. The end of surgery is defined as time of last suture.

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

End point timeframe:

After start of first IMP administration until end of surgery.

| End point values                     | BT524               | FFP/Cryo            |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 107 <sup>[10]</sup> | 104 <sup>[11]</sup> |  |  |
| Units: mL                            |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Cell salvage                         | 95.6 (± 244.57)     | 78.0 (± 234.77)     |  |  |
| Allogeneic platelets                 | 3.0 (± 30.94)       | 3.6 (± 36.38)       |  |  |
| Allogeneic RBCs                      | 455.5 (± 492.19)    | 488.4 (± 547.72)    |  |  |
| Allogeneic FFP                       | 60.5 (± 217.68)     | 14.8 (± 110.94)     |  |  |
| Cryoprecipitate                      | 0 (± 0)             | 0 (± 0)             |  |  |

Notes:

[10] - mFAS

[11] - mFAS

## Statistical analyses

**Secondary: Amount of Red Blood Cells**

|   |                           |
|---|---------------------------|
| End point title   | Amount of Red Blood Cells |
| End point description:<br>Amount (volume) of red blood cells (RBCs) (allogeneic and autologous) infused after start of first IMP administration until end of surgery. The end of surgery is defined as time of last suture. |                           |
| End point type  | Secondary                 |
| End point timeframe:<br>After start of first IMP administration until end of surgery.   |                           |

| End point values                             | BT524                    | FFP/Cryo                 |  |  |
|--|--------------------------|--------------------------|--|--|
| Subject group type                           | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed                  | 107 <sup>[12]</sup>      | 104 <sup>[13]</sup>      |  |  |
| Units: mL                                    |                          |                          |  |  |
| least squares mean (confidence interval 95%) | 543.4 (441.99 to 644.77) | 558.9 (456.08 to 661.62) |  |  |

Notes:

[12] - mFAS

[13] - mFAS

**Statistical analyses**

|  |                         |
|--|-------------------------|
| <b>Statistical analysis title</b>  | Amount of RBCs          |
| Statistical analysis description:<br>An ANOVA analysis will be performed with the amount of RBCs required as the dependent variable and the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. The least square means and difference in least square means will be presented with the corresponding 95% confidence intervals and 2-sided p-value. |                         |
| Comparison groups  | FFP/Cryo v BT524        |
| Number of subjects included in analysis  | 211                     |
| Analysis specification   | Pre-specified           |
| Analysis type  | other <sup>[14]</sup>   |
| P-value  | < 0.831 <sup>[15]</sup> |
| Method   | ANOVA                   |
| Parameter estimate   | Difference in LSM       |
| Point estimate   | -15.5                   |
| Confidence interval  |                         |
| level  | 95 %                    |
| sides  | 2-sided                 |
| lower limit  | -157.83                 |
| upper limit  | 126.88                  |

Notes:

[14] - Difference of LS Mean (BT524-FFP/Cryo)

[15] - LS means, confidence intervals, difference, and p-values are from an ANOVA model with the amount of RBCs required as the dependent variable and the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate.

**Secondary: Post-operative Blood Loss**

|                 |                           |
|-----------------|---------------------------|
| End point title | Post-operative Blood Loss |
|-----------------|---------------------------|

End point description:

Post-operative blood loss in the first 24 hours after end of surgery.

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

End point timeframe:

From end of surgery until 24 hours after the end of surgery.

| End point values                             | BT524                    | FFP/Cryo                 |  |  |
|--|--------------------------|--------------------------|--|--|
| Subject group type                           | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed                  | 107 <sup>[16]</sup>      | 104 <sup>[17]</sup>      |  |  |
| Units: mL                                    |                          |                          |  |  |
| least squares mean (confidence interval 95%) | 306.3 (234.15 to 378.38) | 293.9 (220.76 to 366.95) |  |  |

Notes:

[16] - mFAS

[17] - mFAS

## Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Post-operative Blood Loss |
|----------------------------|---------------------------|

Statistical analysis description:

The post-operative blood loss is the blood loss from end of surgery until 24 hours after end of surgery. This endpoint was descriptively summarized by treatment arm. An ANOVA analysis was performed with the post-operative blood loss in the first 24 hours as the dependent variable and the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. The LSM and difference between groups was presented with corresponding 95% confidence intervals and 2-sided p-value.

|   |                   |
|---|-------------------|
| Comparison groups                       | BT524 v FFP/Cryo  |
| Number of subjects included in analysis | 211               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.809           |
| Method                                  | ANOVA             |
| Parameter estimate                      | Difference in LSM |
| Point estimate                          | 12.4              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | -88.84            |
| upper limit                             | 113.66            |

## Secondary: Subjects with Rebleeds

|                 |                        |
|-----------------|------------------------|
| End point title | Subjects with Rebleeds |
|-----------------|------------------------|

End point description:

Proportion (%) of subjects with rebleeds after the end of surgery until day 8.

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

End point timeframe:

After the end of surgery until day 8.

| End point values            | BT524               | FFP/Cryo            |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 107 <sup>[18]</sup> | 104 <sup>[19]</sup> |  |  |
| Units: Number of subjects   | 0                   | 5                   |  |  |

Notes:

[18] - mFAS

[19] - mFAS

## Statistical analyses

| Statistical analysis title              | Subjects with Rebleeds   |
|---|--------------------------|
| Comparison groups                       | BT524 v FFP/Cryo         |
| Number of subjects included in analysis | 211                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[20]</sup>    |
| P-value                                 | = 0.022 <sup>[21]</sup>  |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Difference in proportion |
| Point estimate                          | -4.8                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -8.9                     |
| upper limit                             | -0.7                     |

Notes:

[20] - The proportion of subjects with rebleeds is compared between the treatment arms using a CMH approach stratified by predictive blood loss. The number and percentage of subjects with a rebleed were presented and the estimated treatment effect (difference in rebleed rate between treatment arms), corresponding 95% confidence interval, and 2-sided p-value for the difference is presented.

[21] - p-value is from a CMH model stratified by predictive blood loss

## Secondary: Hospital length of stay after surgery

| End point title   | Hospital length of stay after surgery |
|---|---------------------------------------|
| End point description:  |                                       |
| Length of stay after surgery (days) = date of hospital discharge – date of surgery. Where date of discharge is the date of discharge following the IMP treated surgery. |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| From date of surgery until date of hospital discharge.  |                                       |

| End point values            | BT524               | FFP/Cryo            |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 107 <sup>[22]</sup> | 104 <sup>[23]</sup> |  |  |
| Units: Number of subjects   |                     |                     |  |  |
| > 36 days                   | 7                   | 4                   |  |  |
| 29-36 days                  | 4                   | 10                  |  |  |



|            |    |    |  |  |
|------------|----|----|--|--|
| 22-28 days | 13 | 12 |  |  |
| 15-21 days | 34 | 17 |  |  |
| 8-14 days  | 39 | 49 |  |  |
| 1-7 days   | 10 | 12 |  |  |

Notes:

[22] - mFAS

[23] - mFAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: In-hospital mortality

|                 |                       |
|-----------------|-----------------------|
| End point title | In-hospital mortality |
|-----------------|-----------------------|

End point description:

The number and percentages of subjects who died during their hospital stay presented with corresponding 95% confidence intervals of death rate by treatment arm using the Clopper-Pearson Method.

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

End point timeframe:

From day of surgery until hospital discharge.

|                             |                     |                     |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>     | BT524               | FFP/Cryo            |  |  |
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 107 <sup>[24]</sup> | 104 <sup>[25]</sup> |  |  |
| Units: Number of subjects   | 0                   | 0                   |  |  |

Notes:

[24] - mFAS

[25] - mFAS

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent Adverse Events (TEAEs): during or after administration of IMP until the subject's last trial visit.

Non-TEAEs: after signing the ICF and prior administration of IMP.

Adverse event reporting additional description:

Analyses were focused on TEAEs, defined as any AEs with start during or after administration of IMP until the subject's last trial visit.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | BT524 |
|-----------------------|-------|

Reporting group description:

BT524 is a lyophilized, heat-treated, virus and prion safe human fibrinogen concentrate manufactured from human plasma used as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenaemia.

|                       |          |
|-----------------------|----------|
| Reporting group title | FFP/Cryo |
|-----------------------|----------|

Reporting group description:

Conventional replacement therapy with fresh frozen plasma or cryoprecipitate, used during surgery to supplement fibrinogen in case of bleeding.

| Serious adverse events                            | BT524             | FFP/Cryo          |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events |                   |                   |  |
| subjects affected / exposed                       | 28 / 110 (25.45%) | 41 / 112 (36.61%) |  |
| number of deaths (all causes)                     | 0                 | 1                 |  |
| number of deaths resulting from adverse events    | 0                 | 1                 |  |
| Vascular disorders                                |                   |                   |  |
| Deep vein thrombosis                              |                   |                   |  |
| subjects affected / exposed                       | 1 / 110 (0.91%)   | 3 / 112 (2.68%)   |  |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Hypovolaemic shock                                |                   |                   |  |
| subjects affected / exposed                       | 0 / 110 (0.00%)   | 1 / 112 (0.89%)   |  |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Neurogenic shock                                  |                   |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Phlebitis  |                 |                 |  |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| 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 |                 |                 |  |
| Impaired healing                                     |                 |                 |  |
| subjects affected / exposed                          | 2 / 110 (1.82%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical failure                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Immune system disorders                              |                 |                 |  |
| Anaphylactic reaction                                |                 |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) | 7 / 112 (6.25%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 4 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Seroma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 3 / 112 (2.68%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia postoperative                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 3 / 112 (2.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dural tear                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 110 (2.73%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound dehiscence                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural pain                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder injury                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral injury                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal stoma complication             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural complication                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haematoma                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound complication                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stoma site haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound haematoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrospinal fluid leakage                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 110 (1.82%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (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 / 110 (0.00%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic diathesis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (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                     | 2 / 110 (1.82%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric perforation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileal perforation                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia strangulated                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Decubitus ulcer                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (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 |                 |                 |  |
| Joint range of motion decreased                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 3 / 112 (2.68%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis bacterial                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Soft tissue infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| 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>                     | BT524             | FFP/Cryo          |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 92 / 110 (83.64%) | 93 / 112 (83.04%) |  |
| Investigations  |                   |                   |  |
| Gamma-glutamyltransferase increased                   |                   |                   |  |
| subjects affected / exposed                           | 5 / 110 (4.55%)   | 8 / 112 (7.14%)   |  |
| occurrences (all)                                     | 5                 | 8                 |  |
| Oxygen saturation decreased                           |                   |                   |  |
| subjects affected / exposed                           | 2 / 110 (1.82%)   | 7 / 112 (6.25%)   |  |
| occurrences (all)                                     | 2                 | 8                 |  |
| Injury, poisoning and procedural complications        |                   |                   |  |
| Anaemia postoperative                                 |                   |                   |  |
| subjects affected / exposed                           | 15 / 110 (13.64%) | 6 / 112 (5.36%)   |  |
| occurrences (all)                                     | 15                | 6                 |  |
| Vascular disorders                                    |                   |                   |  |
| Hypotension   |                   |                   |  |
| subjects affected / exposed                           | 23 / 110 (20.91%) | 10 / 112 (8.93%)  |  |
| occurrences (all)                                     | 29                | 14                |  |
| Cardiac disorders                                     |                   |                   |  |
| Tachycardia   |                   |                   |  |
| subjects affected / exposed                           | 19 / 110 (17.27%) | 14 / 112 (12.50%) |  |
| occurrences (all)                                     | 22                | 14                |  |
| Blood and lymphatic system disorders                  |                   |                   |  |
| Anaemia   |                   |                   |  |
| subjects affected / exposed                           | 12 / 110 (10.91%) | 13 / 112 (11.61%) |  |
| occurrences (all)                                     | 12                | 19                |  |
| Gastrointestinal disorders                            |                   |                   |  |
| Constipation  |                   |                   |  |
| subjects affected / exposed                           | 6 / 110 (5.45%)   | 2 / 112 (1.79%)   |  |
| occurrences (all)                                     | 6                 | 2                 |  |
| Nausea  |                   |                   |  |
| subjects affected / exposed                           | 10 / 110 (9.09%)  | 4 / 112 (3.57%)   |  |
| occurrences (all)                                     | 11                | 4                 |  |
| Hepatobiliary disorders                               |                   |                   |  |
| Hypertransaminasaemia                                 |                   |                   |  |
| subjects affected / exposed                           | 13 / 110 (11.82%) | 11 / 112 (9.82%)  |  |
| occurrences (all)                                     | 13                | 11                |  |

|   |  |  |  |
|---|--|--|--|
| Respiratory, thoracic and mediastinal disorders<br>Pneumothorax<br>subjects affected / exposed<br>occurrences (all)   | 4 / 110 (3.64%)<br>5                                 | 6 / 112 (5.36%)<br>6                                 |  |
| Psychiatric disorders<br>Hallucination<br>subjects affected / exposed<br>occurrences (all)  | 29 / 110 (26.36%)<br>30                              | 26 / 112 (23.21%)<br>26                              |  |
| Infections and infestations<br>Pneumonia<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 10 / 110 (9.09%)<br>10<br><br>10 / 110 (9.09%)<br>10 | 10 / 112 (8.93%)<br>10<br><br>10 / 112 (8.93%)<br>10 |  |
| Metabolism and nutrition disorders<br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)  | 5 / 110 (4.55%)<br>5                                 | 6 / 112 (5.36%)<br>7                                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 26 April 2018    | The amendment clarified the treatment algorithm for allogeneic or autologous blood products (ABPs) administration and specified the need for repeated tests at screening and baseline visits. The prior version lacked clarity on whether the IMP infusion must be finished before ABPs can be given. The amendment specified that certain ABPs and hemostatic agents cannot be administered prior to or during IMP treatment, except for red blood cells. |
| 07 June 2019     | The amendment adjusted the intra-operative inclusion criterion, changing the trigger for IMP treatment from > 1000 mL blood loss to approximately 1 L based on the clinical need for fibrinogen supplementation. Blood loss estimation, not measurement, should trigger treatment. Dosage was revised to avoid under-dosing with BT524 and to allow repeated IMP dosing.   |
| 04 December 2019 | The amendment expanded the trial's scope to include UK-based abdominal surgery cases, introducing cryoprecipitate as a BT524 comparator. Biostatistical changes encompassed three interim analyses and post Data Monitoring adjustments to standard deviation and power.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported