



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
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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:

Population of trial subjects

Subjects enrolled per country

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:

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)	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
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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.

Arm title	FFP/Cryo
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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.

Number of subjects in period 1^[1]	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: 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: 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: 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: 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 ≥ 18			
Units: years			
arithmetic mean	60.9		
standard deviation	± 12.95		
Gender categorical			
Units: Subjects			
Female	115		
Male	86		

End points

End points 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 hypofibrinogenemia.	
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.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: 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: 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.	

Primary: Intra-operative blood loss

End point title	Intra-operative blood loss
End point description: 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: 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 ^[1]	98 ^[2]		
Units: mL				
least squares mean (confidence interval 95%)	1380.70 (1187.09 to 1574.31)	1660.13 (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 ^[3]
P-value	< 0.001 ^[4]
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 ^[5]	102 ^[6]		
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 ^[7]
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 ^[8]	104 ^[9]		
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

Statistical analysis title	Time to first Correction of Fibrinogen level
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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
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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
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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 ^[10]	104 ^[11]		
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: 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: 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 ^[12]	104 ^[13]		
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

Statistical analysis title	Amount of RBCs
Statistical analysis description: 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 ^[14]
P-value	< 0.831 ^[15]
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
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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 ^[16]	104 ^[17]		
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 ^[18]	104 ^[19]		
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 ^[20]
P-value	= 0.022 ^[21]
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 ^[22]	104 ^[23]		
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
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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
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End point timeframe:

From day of surgery until hospital discharge.

End point values	BT524	FFP/Cryo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107 ^[24]	104 ^[25]		
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	BT524
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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
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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 %

Non-serious adverse events	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 Pneumothorax subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 5	6 / 112 (5.36%) 6	
Psychiatric disorders Hallucination subjects affected / exposed occurrences (all)	29 / 110 (26.36%) 30	26 / 112 (23.21%) 26	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 10 10 / 110 (9.09%) 10	10 / 112 (8.93%) 10 10 / 112 (8.93%) 10	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	5 / 110 (4.55%) 5	6 / 112 (5.36%) 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported