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Efficacy and Safety Study of BERIPLEX® P/N (Kcentra) Compared With Plasma in Patients With Acute Major Bleeding Caused by Anticoagulant Therapy

This study has been completed.

Sponsor:
CSL Behring

Information provided by (Responsible Party):
CSL Behring

ClinicalTrials.gov Identifier:
NCT00708435

First received: July 1, 2008
Last updated: January 1, 2014
Last verified: September 2013
History of Changes

Full Text View | Tabular View | **Study Results** | Disclaimer | How to Read a Study Record

Results First Received: June 7, 2013

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
Conditions:	Blood Coagulation Disorders Acute Major Bleeding
Interventions:	Biological: Beriplex® P/N (Kcentra) Biological: Fresh frozen plasma

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Single intravenous infusion as required to treat acute major bleeding; dosage 25, 35 or 50 units/kg depending on baseline INR, amount of coagulation factor IX and body weight.

Fresh Frozen Plasma	Fresh frozen plasma : Single intravenous infusion as required to treat acute major bleeding; dosage 10, 12, or 15 mL/kg depending on baseline INR and body weight.

Participant Flow: Overall Study

	Beriplex® P/N	Fresh Frozen Plasma
STARTED	**107**	**109**
COMPLETED	**82** [1]	**92** [1]
NOT COMPLETED	**25**	**17**
Death / Serious Adverse Event	**10**	**5**
Lost to Follow-up	**9**	**4**
Withdrawal by Subject	**3**	**7**
Adverse Event	**1**	**0**
Protocol Violation	**0**	**1**
Intervention by primary care physician	**1**	**0**
Refused hospitalization	**1**	**0**

[1] These data are 'on-study' results collected up to the subject's Day 45 visit.

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The Intention-to-treat population comprised all subjects who were (1) eligible for the study and had (2) signed informed consent and were randomized to 1 of the 2 treatment groups regardless of whether the subjects received study product. In the ITT population, subjects were analyzed “as randomized”.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight
Total	Total of all reporting groups

Baseline Measures

	Beriplex® P/N	Fresh Frozen Plasma	Total
Overall Participants [units: participants]	**107**	**109**	**216**
Age, Customized [units: Participants]			
< 65 years	**36**	**32**	**68**
≥ 65 to < 75 years	**28**	**29**	**57**
≥ 75 years	**43**	**48**	**91**
Gender			

[units: participants]			
Female	**52**	**55**	**107**
Male	**55**	**54**	**109**

Outcome Measures

Hide All Outcome Measures

1. Primary: Percentage of Participants Achieving Hemostatic Efficacy of Stopping an Ongoing Major Bleed [Time Frame: At 1 and 4 hours after the end of infusion]

Measure Type	Primary
Measure Title	Percentage of Participants Achieving Hemostatic Efficacy of Stopping an Ongoing Major Bleed
Measure Description	Hemostatic efficacy was determined by a blinded independent board as excellent, good, or poor/none, based on prespecified definitions. Assessments of visible or non-visible musculoskeletal bleeding were made at 1 and 4 hours after the end of infusion. Hemostatic efficacy was the binary endpoint of effective or non-effective hemostasis, where 'effective' was a hemostatic efficacy rating of "excellent" or "good," and 'non-effective' was a hemostatic efficacy rating of "poor/none".
Time Frame	At 1 and 4 hours after the end of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The Intention-to-Treat Efficacy (ITT-E) population included all randomized participants who had received any study product, presented with acute major bleeding, and had an international normalized ratio (INR) > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**98**	**104**
Percentage of Participants Achieving Hemostatic Efficacy of Stopping an Ongoing Major Bleed [units: percentage of participants] Number (95% Confidence Interval)	**72.4** **(63.6 to 81.3)**	**65.4** **(56.2 to 74.5)**

Statistical Analysis 1 for Percentage of Participants Achieving Hemostatic Efficacy of Stopping an Ongoing Major Bleed

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	95% confidence interval

Difference in effective hemostasis (%) [4]	7.1
95% Confidence Interval	-5.8 to 19.9

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	The analysis of hemostatic efficacy was via calculation of the 95% confidence interval (CI) for the difference (Beriplex minus plasma) in the percentage of participants with effective hemostasis.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	The non-inferiority margin was −(minus)10%. If the lower limit of the 2-sided 95% CI was >–10%, then the null-hypothesis was rejected and it was concluded that Beriplex was non-inferior to plasma. The sample size estimation assumed that hemostatic efficacy would be rated 'effective' in 85% of participants in the plasma group and 90% of participants in the Beriplex group. The power to show non-inferiority with these assumptions was greater than 80% for two treatment groups of 83 participants.
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	Farrington and Manning's method was used to estimate the 95% CI for the difference in the percentage of participants with hemostasis.
[4]	Other relevant estimation information:
	Both primary endpoints had to be non-inferior for Beriplex to be non-inferior. There is no P-value as non-inferiority was assessed via the 95% CI calculation for the difference (Beriplex minus plasma) in the % of subjects with effective hemostasis.

2. Primary: Percentage of Participants Who Had a Rapid Decrease of the International Normalized Ratio (INR) [Time Frame: 30 minutes after end of infusion]

Measure Type	Primary
Measure Title	Percentage of Participants Who Had a Rapid Decrease of the International Normalized Ratio (INR)
Measure Description	A rapid decrease of the international normalized ratio (INR) was defined as an INR ≤ 1.3 at 30 minutes after the end of the infusion. The INR is a standard way to describe the time it takes for blood to clot; an INR range of 0.8 to 1.2 is considered normal for a healthy person who is not using oral anticoagulant therapy.
Time Frame	30 minutes after end of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**

Overall Participants [units: participants]	**98**	**104**
Percentage of Participants Who Had a Rapid Decrease of the International Normalized Ratio (INR) [units: percentage of participants] Number (95% Confidence Interval)	**62.2** **(52.6 to 71.8)**	**9.6** **(3.9 to 15.3)**

Statistical Analysis 1 for Percentage of Participants Who Had a Rapid Decrease of the International Normalized Ratio (INR)

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	95% confidence interval
Difference in the decrease of INR (%) [4]	52.6
95% Confidence Interval	39.4 to 65.9

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	The analysis of the percentage of participants who had a rapid decrease of the INR was via calculation of the 95% confidence interval (CI) for the difference (Beriplex minus plasma) in the percentage of participants with a rapid decrease of the INR.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	The non-inferiority margin was −(minus)10%. If the lower limit of the 2-sided 95% CI was >-10%, then the null-hypothesis was rejected and it was concluded that Beriplex was non-inferior to plasma. The sample size estimation assumed that hemostatic efficacy would be rated ‘effective’ in 85% of participants in the plasma group and 90% of participants in the Beriplex group. The power to show non-inferiority with these assumptions was greater than 80% for two treatment groups of 83 participants.
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	Farrington and Manning's method was used to estimate the 95% CI for the difference in the percentage of participants with a rapid decrease of the INR.
[4]	Other relevant estimation information:
	Both primary endpoints had to be non-inferior for Beriplex to be non-inferior. There is no P-value as non-inferiority was assessed via the 95% CI for the difference (Beriplex minus plasma) in the % of subjects with a rapid decrease of the INR.

3. Secondary: Percentage of Participants Who Had Hemostatic Efficacy for Visible or Non-visible Musculoskeletal Bleeding [Time Frame: At 3 and 6 hours after the start of infusion]

Measure Type	Secondary
Measure Title	Percentage of Participants Who Had Hemostatic Efficacy for Visible or Non-visible Musculoskeletal Bleeding
Measure Description	Hemostatic efficacy was determined by a blinded independent board as excellent, good, or poor/none, based on prespecified definitions. Assessments of visible or non-visible musculoskeletal bleeding were made at 3 and 6 hours after the start of infusion. Hemostatic efficacy was the binary endpoint of effective or non-effective hemostasis, where ‘effective’ was a hemostatic efficacy rating of “excellent” or “good,” and ‘non-effective’ was a hemostatic efficacy rating of “poor/none”.
Time Frame	At 3 and 6 hours after the start of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	Fresh Frozen Plasma
Overall Participants [units: participants]	**98**	**104**
Percentage of Participants Who Had Hemostatic Efficacy for Visible or Non-visible Musculoskeletal Bleeding [units: percentage of participants] Number (95% Confidence Interval)	**73.5** **(64.7 to 82.2)**	**67.3** **(58.3 to 76.3)**

No statistical analysis provided for Percentage of Participants Who Had Hemostatic Efficacy for Visible or Non-visible Musculoskeletal Bleeding

4. Secondary: Incremental in Vivo Recovery (IVR) (Response) of Factors II, VII, IX, and X, Protein C, and Protein S for Beriplex [Time Frame: Before infusion and up to 3 h after the start of infusion]

Measure Type	Secondary
Measure Title	Incremental in Vivo Recovery (IVR) (Response) of Factors II, VII, IX, and X, Protein C, and Protein S for Beriplex
Measure Description	The incremental IVR [(IU/dL)/(IU/kg)] was calculated as follows: (IU/dL activity rise in plasma)/(IU/kg body weight infused) = [maximum increase in component plasma level within 3 hours compared to pre-infusion (IU/dL)]/{[exact dose of component in drug administered (IU)]/[body weight (kg)]}.
Time Frame	Before infusion and up to 3 h after the start of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight

Measured Values

	Beriplex® P/N

Overall Participants [units: participants]	**97**
Incremental in Vivo Recovery (IVR) (Response) of Factors II, VII, IX, and X, Protein C, and Protein S for Beriplex [units: (IU/dL)/(IU/kg body weight)] Mean (Standard Deviation)	
Factor II	**2.00 (0.879)**
Factor VII	**2.15 (2.958)**
Factor IX	**1.29 (0.711)**
Factor X	**1.96 (0.871)**
Protein C	**2.04 (0.958)**
Protein S	**2.17 (1.661)**

No statistical analysis provided for Incremental in Vivo Recovery (IVR) (Response) of Factors II, VII, IX, and X, Protein C, and Protein S for Beriplex

5. Secondary: Plasma Levels of Factors II, VII, IX, and X, Protein C, and Protein S [Time Frame: From preinfusion until 24 h after the start of infusion]

Measure Type	Secondary
Measure Title	Plasma Levels of Factors II, VII, IX, and X, Protein C, and Protein S
Measure Description	Plasma levels are presented as the percentage of normal at pre-infusion and 30 min and 24 h after the start of infusion. The plasma level assay results are reported as a potency relative to a standard, where 100% is considered to be normal.
Time Frame	From preinfusion until 24 h after the start of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**98**	**104**
Plasma Levels of Factors II, VII, IX, and X, Protein C, and Protein S [units: percentage of normal] Mean (Standard Deviation)		
Factor II, pre-infusion (n = 98; 103)	**20.1 (14.56)**	**22.3 (22.39)**

Factor II, 0.5 h after infusion start (n = 88; 90)	**87.5 (44.48)**	**31.9 (22.55)**
Factor II, 24 h after infusion start (n = 92; 99)	**77.1 (22.06)**	**58.1 (19.55)**
Factor VII, pre-infusion (n = 98; 103)	**25.9 (35.01)**	**23.5 (23.45)**
Factor VII, 0.5h after infusion start (n = 88; 90)	**60.5 (45.23)**	**34.6 (26.18)**
Factor VII, 24 h after infusion start (n = 92; 99)	**114.8 (165.28)**	**101.3 (79.01)**
Factor IX, pre-infusion (n = 98; 103)	**36.1 (22.56)**	**39.0 (27.56)**
Factor IX, 0.5 h after infusion start (n = 88; 90)	**76.8 (35.47)**	**47.7 (26.78)**
Factor IX, 24 h after infusion start (n = 92; 99)	**88.5 (35.65)**	**93.0 (29.95)**
Factor X, pre-infusion (n = 98; 102)	**13.0 (11.25)**	**14.7 (18.83)**
Factor X, 0.5 h after infusion start (n = 88; 90)	**99.8 (56.07)**	**23.9 (20.40)**
Factor X, 24 h after infusion start (n = 92; 99)	**83.7 (27.05)**	**58.2 (21.78)**
Protein C, pre-infusion (n = 98; 103)	**39.3 (17.15)**	**41.1 (18.84)**
Protein C, 0.5 h after infusion start (n = 88; 90)	**110.3 (47.37)**	**50.9 (24.78)**
Protein C, 24h after infusion start (n = 92; 98)	**90.3 (27.19)**	**82.8 (24.34)**
Protein S, pre-infusion (n = 97; 102)	**27.8 (11.34)**	**29.6 (12.97)**
Protein S, 0.5 h after infusion start (n = 88; 89)	**59.4 (28.56)**	**38.6 (20.45)**
Protein S, 24 h after infusion start (n = 91; 97)	**47.8 (16.54)**	**45.4 (16.00)**

No statistical analysis provided for Plasma Levels of Factors II, VII, IX, and X, Protein C, and Protein S

6. Secondary: Percentage of Participants With INR Correction at Various Times After the Start of Infusion [Time Frame: From the start of infusion until INR correction; calculated at 0.5, 1, 3, 6, 12, and 24 h after the start of infusion.]

Measure Type	Secondary
Measure Title	Percentage of Participants With INR Correction at Various Times After the Start of Infusion
Measure Description	The time taken from the start of infusion to INR correction (defined as an INR ≤ 1.3) was recorded. The percentage of participants with INR correction was calculated at 0.5, 1, 3, 6, 12, and 24 h after the start of infusion.
Time Frame	From the start of infusion until INR correction; calculated at 0.5, 1, 3, 6, 12, and 24 h after the start of infusion.
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**98**	**104**

Percentage of Participants With INR Correction at Various Times After the Start of Infusion [units: percentage of participants]		
0.5 h	**4**	**0**
1 h	**69**	**0**
3 h	**71**	**9**
6 h	**78**	**16**
12 h	**80**	**36**
24 h	**88**	**58**

No statistical analysis provided for Percentage of Participants With INR Correction at Various Times After the Start of Infusion

7. Secondary: Percentage of Participants With INR Correction at Various Times After Randomization [Time Frame: From randomization until INR correction; calculated at 2.5, 3, 5, 8, 14, and 26 h after randomization.]

Measure Type	Secondary
Measure Title	Percentage of Participants With INR Correction at Various Times After Randomization
Measure Description	The time taken from randomization to INR correction (defined as an INR ≤ 1.3) was recorded. The percentage of participants with INR correction was calculated at 2.5, 3, 5, 8, 14, and 26 h after randomization.
Time Frame	From randomization until INR correction; calculated at 2.5, 3, 5, 8, 14, and 26 h after randomization.
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**98**	**104**
Percentage of Participants With INR Correction at Various Times After Randomization [units: percentage of participants]		
2.5 h	**59**	**2**
3 h	**67**	**2**
5 h	**76**	**10**
8 h	**79**	**22**
14 h	**84**	**38**
26 h	**90**	**70**

No statistical analysis provided for Percentage of Participants With INR Correction at Various Times After Randomization

8. Secondary: Transfusion of Red Blood Cells [Time Frame: From the start of infusion until 24 h after the start of infusion]

Measure Type	Secondary
Measure Title	Transfusion of Red Blood Cells
Measure Description	Red blood cells were packed red blood cells (PRBCs).
Time Frame	From the start of infusion until 24 h after the start of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**98**	**104**
Transfusion of Red Blood Cells [units: Units of PRBCs] Mean (Standard Deviation)	**1.4 (1.77)**	**1.2 (1.57)**

No statistical analysis provided for Transfusion of Red Blood Cells

9. Secondary: Use of Other Blood Products and Hemostatic Agents [Time Frame: From the start of infusion until 24 h after the start of infusion]

Measure Type	Secondary
Measure Title	Use of Other Blood Products and Hemostatic Agents
Measure Description	Other blood products and hemostatic agents containing coagulation factors (such as whole blood, plasma, albumin, platelets) not including PRBCs.
Time Frame	From the start of infusion until 24 h after the start of infusion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	Fresh Frozen Plasma
Overall Participants [units: participants]	**98**	**104**
Use of Other Blood Products and Hemostatic Agents [units: Units of blood products] Mean (Standard Deviation)	**0.3 (1.36)**	**0.3 (0.87)**

No statistical analysis provided for Use of Other Blood Products and Hemostatic Agents

10. Secondary: 45-Day All-cause Mortality [Time Frame: Until Day 45]

Measure Type	Secondary
Measure Title	45-Day All-cause Mortality
Measure Description	No text entered.
Time Frame	Until Day 45
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-E population included all randomized participants who had received any study product, presented with acute major bleeding, and had an INR > 1.3 prior to the infusion. Participants in the ITT-E population were analyzed 'as randomized'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	Fresh Frozen Plasma
Overall Participants [units: participants]	**98**	**104**

45-Day All-cause Mortality [units: participants]	**9**	**5**

No statistical analysis provided for 45-Day All-cause Mortality

11. Secondary: Overall Treatment-emergent Adverse Events (TEAEs) [Time Frame: From the start of infusion up to the allowed time window of the Day 10 visit for non-serious AEs and from the start of infusion up to the allowed time window of the Day 45 visit for SAEs.]

Measure Type	Secondary
Measure Title	Overall Treatment-emergent Adverse Events (TEAEs)
Measure Description	Number of participants with TEAEs. Treatment-related AEs were defined as events whose relationship to study treatment was definitely related, probably related, or possibly related in the opinion of the investigator. AEs with missing relationship were considered related to treatment. Serious TEAEs were treatment-emergent SAEs. Deaths reported up to and including Day 45; one additional Beriplex death occurred after Day 45.
Time Frame	From the start of infusion up to the allowed time window of the Day 10 visit for non-serious AEs and from the start of infusion up to the allowed time window of the Day 45 visit for SAEs.
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The ITT-S population included all participants who were randomized and who had received any portion of study product. Participants in the ITT-S population were analyzed 'as treated'.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N: Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma: Intravenous Infusion, dosage depending on baseline INR and body weight

Measured Values

	Beriplex® P/N	**Fresh Frozen Plasma**
Overall Participants [units: participants]	**103**	**109**
Overall Treatment-emergent Adverse Events (TEAEs) [units: participants]		
Any TEAE	**66**	**71**
At least possibly treatment-related TEAE	**10**	**23**
Serious TEAE	**32**	**26**
Death	**10**	**5**

No statistical analysis provided for Overall Treatment-emergent Adverse Events (TEAEs)

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	From the start of infusion up to the allowed time window of the Day 45 visit for SAEs, and from the start of infusion up to the allowed time window of the Day 10 visit for non-serious AEs.
Additional Description	The AEs presented were treatment-emergent AEs (TEAEs). The ITT-S population included all subjects who were randomized and who had received any portion of study product. Participants in the ITT-S population were analyzed 'as treated'. "General disorders" were collected under the MedDRA SOC General disorders and administration site conditions.

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight

Serious Adverse Events

	Beriplex® P/N	Fresh Frozen Plasma
Total, serious adverse events		
# participants affected / at risk	**32/103 (31.07%)**	**26/109 (23.85%)**
Blood and lymphatic system disorders		
Anaemia † 1		
# participants affected / at risk	**0/103 (0.00%)**	**2/109 (1.83%)**
# events	**0**	**2**
Haemorrhagic anaemia † 1		
# participants affected / at risk	**0/103 (0.00%)**	**1/109 (0.92%)**
# events	**0**	**1**
Cardiac disorders		
Atrial flutter † 1		
# participants affected / at risk	**2/103 (1.94%)**	**0/109 (0.00%)**
# events	**2**	**0**
Cardiac failure † 1		
# participants affected / at risk	**1/103 (0.97%)**	**1/109 (0.92%)**
# events	**1**	**1**
Myocardial ischaemia † 1		
# participants affected / at risk	**0/103 (0.00%)**	**2/109 (1.83%)**
# events	**0**	**2**
Cardiac failure chronic † 1		
# participants affected / at risk	**0/103 (0.00%)**	**1/109 (0.92%)**
# events	**0**	**2**
Cardio-respiratory arrest † 1		
# participants affected / at risk	**1/103 (0.97%)**	**0/109 (0.00%)**
# events	**1**	**0**
Sinus bradycardia † 1		
# participants affected / at risk	**1/103 (0.97%)**	**0/109 (0.00%)**
# events	**1**	**0**
Cardiac failure congestive † 1		
# participants affected / at risk	**1/103 (0.97%)**	**4/109 (3.67%)**

# events	1	5
Myocardial infarction † 1		
# participants affected / at risk	1/103 (0.97%)	1/109 (0.92%)
# events	1	1
Gastrointestinal disorders		
Gastrointestinal haemorrhage † 1		
# participants affected / at risk	1/103 (0.97%)	1/109 (0.92%)
# events	1	1
Diarrhoea † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Diverticulum intestinal haemorrhagic † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Gastrooesophageal reflux disease † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Small intestinal obstruction † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
General disorders		
Sudden death † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Hepatobiliary disorders		
Cholecystitis chronic † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Hepatic failure † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Liver disorder † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Infections and infestations		
Pneumonia † 1		
# participants affected / at risk	2/103 (1.94%)	1/109 (0.92%)
# events	2	1
Bacteraemia † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Cellulitis † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Gastroenteritis † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Infection † 1		

# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Septic shock † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Staphylococcal sepsis † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Urinary tract infection † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Device dislocation † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Spinal fracture † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Subdural haematoma † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Metabolism and nutrition disorders		
Dehydration † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Fluid overload † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Hypoglycaemia † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Musculoskeletal and connective tissue disorders		
Intervertebral disc degeneration † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lung cancer metastatic † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Lung carcinoma cell type unspecified stage iv † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Metastases to liver † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Oesophageal adenocarcinoma † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0

Pancreatic carcinoma † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Nervous system disorders		
Ischaemic stroke † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Encephalopathy † 1		
# participants affected / at risk	0/103 (0.00%)	2/109 (1.83%)
# events	0	2
Haemorrhage intracranial † 1		
# participants affected / at risk	2/103 (1.94%)	0/109 (0.00%)
# events	2	0
Subarachnoid haemorrhage † 1		
# participants affected / at risk	0/103 (0.00%)	2/109 (1.83%)
# events	0	2
Cerebrovascular accident † 1		
# participants affected / at risk	0/103 (0.00%)	1/109 (0.92%)
# events	0	1
Convulsion † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Headache † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Renal and urinary disorders		
Renal failure acute † 1		
# participants affected / at risk	1/103 (0.97%)	1/109 (0.92%)
# events	1	1
Respiratory, thoracic and mediastinal disorders		
Respiratory failure † 1		
# participants affected / at risk	2/103 (1.94%)	1/109 (0.92%)
# events	2	1
Pleural effusion † 1		
# participants affected / at risk	1/103 (0.97%)	1/109 (0.92%)
# events	1	1
Respiratory distress † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Vascular disorders		
Deep vein thrombosis † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	2	0
Haematoma † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0
Peripheral vascular disorder † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)

# events	1	0
Shock haemorrhagic † 1		
# participants affected / at risk	1/103 (0.97%)	0/109 (0.00%)
# events	1	0

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 12.0

Other Adverse Events

Hide Other Adverse Events

Time Frame	From the start of infusion up to the allowed time window of the Day 45 visit for SAEs, and from the start of infusion up to the allowed time window of the Day 10 visit for non-serious AEs.
Additional Description	The AEs presented were treatment-emergent AEs (TEAEs). The ITT-S population included all subjects who were randomized and who had received any portion of study product. Participants in the ITT-S population were analyzed 'as treated'. "General disorders" were collected under the MedDRA SOC General disorders and administration site conditions.

Frequency Threshold

Threshold above which other adverse events are reported	2

Reporting Groups

	Description
Beriplex® P/N	Beriplex® P/N : Intravenous infusion, dosage depending on baseline INR, amount of coagulation factor IX and body weight
Fresh Frozen Plasma	Fresh frozen plasma : Intravenous Infusion, dosage depending on baseline INR and body weight

Other Adverse Events

	Beriplex® P/N	Fresh Frozen Plasma
Total, other (not including serious) adverse events		
# participants affected / at risk	46/103 (44.66%)	40/109 (36.70%)
Cardiac disorders		
Tachycardia † 1		
# participants affected / at risk	4/103 (3.88%)	1/109 (0.92%)
# events	4	1
Bradycardia † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Gastrointestinal disorders		
Constipation † 1		
# participants affected / at risk	5/103 (4.85%)	8/109 (7.34%)
# events	5	8
Diarrhoea † 1		
# participants affected / at risk	0/103 (0.00%)	4/109 (3.67%)
# events	0	4
Nausea † 1		
# participants affected / at risk	2/103 (1.94%)	3/109 (2.75%)

# events	2	3
Vomiting † 1		
# participants affected / at risk	3/103 (2.91%)	2/109 (1.83%)
# events	3	2
General disorders		
Oedema peripheral † 1		
# participants affected / at risk	6/103 (5.83%)	7/109 (6.42%)
# events	6	7
Pyrexia † 1		
# participants affected / at risk	4/103 (3.88%)	4/109 (3.67%)
# events	4	4
Chest pain † 1		
# participants affected / at risk	2/103 (1.94%)	3/109 (2.75%)
# events	2	3
Infections and infestations		
Urinary tract infection † 1		
# participants affected / at risk	3/103 (2.91%)	3/109 (2.75%)
# events	3	3
Injury, poisoning and procedural complications		
Skin laceration † 1		
# participants affected / at risk	4/103 (3.88%)	0/109 (0.00%)
# events	4	0
Investigations		
International normalised ratio increased † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Metabolism and nutrition disorders		
Hypokalaemia † 1		
# participants affected / at risk	2/103 (1.94%)	6/109 (5.50%)
# events	2	6
Hyperkalaemia † 1		
# participants affected / at risk	3/103 (2.91%)	3/109 (2.75%)
# events	3	3
Fluid overload † 1		
# participants affected / at risk	0/103 (0.00%)	3/109 (2.75%)
# events	0	3
Hypoglycaemia † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Hypomagnesaemia † 1		
# participants affected / at risk	1/103 (0.97%)	3/109 (2.75%)
# events	1	3
Hypophosphataemia † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Musculoskeletal and connective tissue disorders		
Arthralgia † 1		

# participants affected / at risk	4/103 (3.88%)	1/109 (0.92%)
# events	4	1
Nervous system disorders		
Headache † 1		
# participants affected / at risk	10/103 (9.71%)	4/109 (3.67%)
# events	10	4
Dizziness † 1		
# participants affected / at risk	4/103 (3.88%)	0/109 (0.00%)
# events	4	0
Psychiatric disorders		
Insomnia † 1		
# participants affected / at risk	6/103 (5.83%)	3/109 (2.75%)
# events	6	3
Anxiety † 1		
# participants affected / at risk	4/103 (3.88%)	2/109 (1.83%)
# events	4	2
Agitation † 1		
# participants affected / at risk	3/103 (2.91%)	1/109 (0.92%)
# events	3	1
Mental status change † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Respiratory, thoracic and mediastinal disorders		
Pulmonary oedema † 1		
# participants affected / at risk	2/103 (1.94%)	4/109 (3.67%)
# events	3	4
Pleural effusion † 1		
# participants affected / at risk	4/103 (3.88%)	0/109 (0.00%)
# events	4	0
Dyspnoea † 1		
# participants affected / at risk	2/103 (1.94%)	3/109 (2.75%)
# events	2	3
Skin and subcutaneous tissue disorders		
Rash † 1		
# participants affected / at risk	2/103 (1.94%)	3/109 (2.75%)
# events	2	3
Ecchymosis † 1		
# participants affected / at risk	3/103 (2.91%)	0/109 (0.00%)
# events	3	0
Vascular disorders		
Hypotension † 1		
# participants affected / at risk	5/103 (4.85%)	3/109 (2.75%)
# events	5	4

† Events were collected by systematic assessment

1 Term from vocabulary, MedDRA 12.0

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data

No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☑ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Restriction Description: CSL agreements and restrictions on publishing may vary with individual investigators; however, CSL will not prohibit any investigator from publishing. CSL supports the publication of results from all centers of a multi-center trial and generally requires that reports based on single-site data not precede the primary publication of the entire clinical trial.

Results Point of Contact:

Name/Title: Clinical Trial Disclosure Manager
Organization: CSL Behring
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e-mail: clinicaltrials@cslbehring.com

Publications of Results:

Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013 Sep 10;128(11):1234-43. doi: 10.1161/CIRCULATIONAHA.113.002283.

Responsible Party:	CSL Behring
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