



Clinical trial results:

A Randomized Controlled Double-Blind Phase 3 Study to Assess Characteristics of S-303 Treated RBC Components and Evaluate Safety and Efficacy in Patients Requiring Transfusion Support of Acute Anemia Summary

EudraCT number	2011-006253-29
Trial protocol	DE
Global end of trial date	10 December 2014

Results information

Result version number	v1 (current)
This version publication date	16 April 2023
First version publication date	16 April 2023

Trial information

Trial identification

Sponsor protocol code	CLI 00070
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01716923
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cerus Corporation
Sponsor organisation address	1220 Concord Avenue, Concord/CA, United States, 94520
Public contact	Carol M.Moore, Cerus Corporation, 1 9258766819, cmoore@cerus.com
Scientific contact	Richard J. Benjamin, MS PhD FRCPATH, Cerus Corporation, 1 9252886020, rbenjamin@cerus.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	10 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2014
Global end of trial reached?	Yes
Global end of trial date	10 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the in vitro characteristics of S-303 treated RBCs suspended in SAG-Mannitol; including mean hemoglobin per RBC component and other biochemical/metabolic properties recognized to correlate with RBC viability.

The secondary objective of the study was to assess the clinical safety and efficacy of S-303 treated RBC components in patients requiring transfusion support for acute anemia (during or shortly after a cardiac surgery).

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice (GCP) according to the International Conference on Harmonization (ICH) guidelines, and local ethical and legal requirements that are consistent with the Declaration of Helsinki. The risks and hazards of study participation were explained to the potential study subjects, under the supervision of a qualified, licensed physician. Written informed consent was obtained from all study subjects prior to any tests or evaluations. A copy of the signed informed consent was provided to each subject and was also maintained in the subject's medical record. Patient confidential information was protected through compliance with study and/or site specific privacy protection procedures. Personal Data of the Study Subjects were handled in accordance with the data protection laws applicable and all study activities were carried out under the Agreement as required by Article 30 of the GDPR.

Background therapy:

All patients were subjected to cardio surgical procedures.

Evidence for comparator:

The study was conducted as a two-group (Test and Control) study consisting of two portions: in vitro and clinical. The in vitro characteristics of the study RBCs were compared to the EDQM criteria for RBCs, leukocyte-depleted in additive solution (Council of Europe Guide for the Preparation, Use and Quality Assurance of Blood Components, 16th edn. Strasbourg, France, Council of Europe Publishing 2010). The clinical safety and efficacy of S-303 treated RBC were compared to conventional RBC when transfused in support of acute anemia during or following cardiac surgery. The study was divided into an acute surgical care period starting at the day of surgery until 7 days post-surgery during which RBC (Test or Control) were administered and a post-surgical follow-up period of a minimum of 90 days to collect additional safety data.

Actual start date of recruitment	26 October 2012
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	Germany: 87
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	7
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Germany at 1 blood center in Frankfurt and 2 clinical centers located in Frankfurt and Bad Nauheim.

Initiation (first patient enrolled): October 26, 2013

Completion (last patient completed): August 7, 2014

Pre-assignment

Screening details:

In order to minimize the number of patients who enrolled in the study but did not require RBC transfusion, only patients with a relatively high likelihood to receive a transfusion as determined by the Investigator, or patients with a Transfusion Risk Understanding Screening Tool (TRUST) Score of 3 or greater were eligible for enrollment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Blinding was achieved by transferring the Control RBC components to a Storage Container identical to the Storage Container used for the Test RBC components processed with the S-303 Treatment System. The labels for Test and Control RBC components were identical. Blood Center personnel involved in processing, preparation, storage, cross-matching, and distribution of study RBC components were not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

S-303 RBC components (Test) were prepared at a licensed Blood Center following training and completion of the S-303 Treatment System for RBC process validation studies. The S-303 treatment process was performed on RBC components prepared from leukocyte reduced whole blood collections. Prior to treatment, a sample of the input RBCs was retained for assessment of RBC in vitro characteristics on Day 0. The S-303 RBC Treatment System consists of 4 components: Processing set, Filter set, Amustaline dihydrochloride (S-303), Glutathione sodium Salt (GSH).

For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Arm type	Experimental
Investigational medicinal product name	INTERCEPT Blood System for Red Blood Cells
Investigational medicinal product code	
Other name	INTERCEPT treated Red Blood Cells
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage (transfusion) depended on Investigators decision and patients actual need (actual Hb/Hematocrit requirement)

Arm title	Control
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Arm description:

The Control RBC components were prepared by conventional methods approved for use in the blood centers participating in the clinical study but were stored in the same type of storage bag as that of the

Test RBCs to facilitate blinding of hospital personnel and clinicians administering the Test and Control RBC units to patients in the clinical study.

For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Arm type	Active comparator
Investigational medicinal product name	Conventional Red Blood Cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Physician decision and patient need (actual Hb/Hematocrit requirement)

Number of subjects in period 1	Test	Control
Started	45	42
Completed	36	37
Not completed	9	5
Adverse event, serious fatal	3	2
Adverse event, non-fatal	1	-
Other	-	3
Patient decision to withdraw	5	-

Baseline characteristics

Reporting groups

Reporting group title	Test
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Reporting group description:

S-303 RBC components (Test) were prepared at a licensed Blood Center following training and completion of the S-303 Treatment System for RBC process validation studies. The S-303 treatment process was performed on RBC components prepared from leukocyte reduced whole blood collections. Prior to treatment, a sample of the input RBCs was retained for assessment of RBC in vitro characteristics on Day 0. The S-303 RBC Treatment System consists of 4 components: Processing set, Filter set, Amustaline dihydrochloride (S-303), Glutathione sodium Salt (GSH).

For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Reporting group title	Control
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Reporting group description:

The Control RBC components were prepared by conventional methods approved for use in the blood centers participating in the clinical study but were stored in the same type of storage bag as that of the Test RBCs to facilitate blinding of hospital personnel and clinicians administering the Test and Control RBC units to patients in the clinical study.

For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Reporting group values	Test	Control	Total
Number of subjects	45	42	87
Age categorical			
Adults: 18-84 years			
Units: Subjects			
Adults (18-64 years)	6	1	7
From 65-84 years	39	41	80
Gender categorical			
Age ≥18 years, of either gender			
Total number of patients			
Test: Female (11) Male (14)			
Control: Female (16) Male (10)			
Units: Subjects			
Female	24	22	46
Male	21	20	41
Surgical Procedure			
Subjects must be scheduled to receive one of the following operative procedures:			
o Coronary artery bypass graft (CABG) only, first procedure			
o Valve repair or replacement only, first procedure			
o A combination of first time CABG and valve repair or replacement			
o Surgery scheduled, but postponed			
Units: Subjects			
CABG surgery	20	20	40
Valve repair or replacement	18	13	31
Combination of CABG and Valve repair	4	5	9
Surgery postponed	3	2	5

Surgery scheduled, patient decided not to proceed	0	2	2
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Subject analysis sets

Subject analysis set title	Intent to Treat (ITT) Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included all randomized patients regardless of surgical or transfusion status.

Subject analysis set title	Modified Intent to Treat (MITT) Group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Included all randomized patients exposed to any on-study RBC components during the study transfusion period (includes patients who were only exposed due to the priming of a cardiopulmonary bypass circuit).

Subject analysis set title	Randomized Non Treated Group
Subject analysis set type	Full analysis

Subject analysis set description:

Included all randomized patients who were not exposed to any on-study RBC components (regardless of surgical status).

Reporting group values	Intent to Treat (ITT) Group	Modified Intent to Treat (MITT) Group	Randomized Non Treated Group
Number of subjects	87	51	36
Age categorical			
Adults: 18-84 years			
Units: Subjects			
Adults (18-64 years)	7	4	3
From 65-84 years	80	47	33
Gender categorical			
Age ≥18 years, of either gender			
Total number of patients			
Test: Female (11) Male (14)			
Control: Female (16) Male (10)			
Units: Subjects			
Female	46	27	19
Male	41	24	17
Surgical Procedure			
Subjects must be scheduled to receive one of the following operative procedures:			
o Coronary artery bypass graft (CABG) only, first procedure			
o Valve repair or replacement only, first procedure			
o A combination of first time CABG and valve repair or replacement			
o Surgery scheduled, but postponed			
Units: Subjects			
CABG surgery	40	25	15
Valve repair or replacement	31	18	13
Combination of CABG and Valve repair	9	8	1
Surgery postponed	5	0	5
Surgery scheduled, patient decided not to proceed	2	0	2

End points

End points reporting groups

Reporting group title	Test
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Reporting group description:

S-303 RBC components (Test) were prepared at a licensed Blood Center following training and completion of the S-303 Treatment System for RBC process validation studies. The S-303 treatment process was performed on RBC components prepared from leukocyte reduced whole blood collections. Prior to treatment, a sample of the input RBCs was retained for assessment of RBC in vitro characteristics on Day 0. The S-303 RBC Treatment System consists of 4 components: Processing set, Filter set, Amustaline dihydrochloride (S-303), Glutathione sodium Salt (GSH). For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Reporting group title	Control
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Reporting group description:

The Control RBC components were prepared by conventional methods approved for use in the blood centers participating in the clinical study but were stored in the same type of storage bag as that of the Test RBCs to facilitate blinding of hospital personnel and clinicians administering the Test and Control RBC units to patients in the clinical study.

For the in vitro portion of the study, RBC components were processed using the Test or Control procedure based on simple randomization. For the clinical portion of the study, anticipated prognostic factors including the clinical site and elective cardiac procedure were balanced using a stratified randomization scheme. Randomized patients who did not require any RBC transfusions during the 7-day transfusion period were replaced.

Subject analysis set title	Intent to Treat (ITT) Group
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Included all randomized patients regardless of surgical or transfusion status.

Subject analysis set title	Modified Intent to Treat (MITT) Group
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Included all randomized patients exposed to any on-study RBC components during the study transfusion period (includes patients who were only exposed due to the priming of a cardiopulmonary bypass circuit).

Subject analysis set title	Randomized Non Treated Group
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Subject analysis set type	Full analysis
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Subject analysis set description:

Included all randomized patients who were not exposed to any on-study RBC components (regardless of surgical status).

Primary: Post-Production Hemoglobin Content

End point title	Post-Production Hemoglobin Content
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End point description:

The primary efficacy endpoint was the hemoglobin content per RBC component derived from the in-vitro portion of the study (grams of hemoglobin per processed component). This endpoint was captured after the INTERCEPT process and after the bag transfer for Test and Control components, respectively. The study employed an equivalence design to test the hypothesis that S-303 treated RBC components (Test) were equivalent to conventional RBC components (Control) with respect to mean grams of hemoglobin per component processed.

End point type	Primary
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End point timeframe:

Post-production

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[1]	26 ^[2]		
Units: g/component				
arithmetic mean (standard deviation)	53.6 (± 5.6)	56.3 (± 6.0)		

Notes:

[1] - Number of test components produced: 389

[2] - Number of control components produced: 365

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	-1.92

Notes:

[3] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component

Secondary: End of Storage Hemoglobin Content

End point title	End of Storage Hemoglobin Content
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

End of Storage (Day 35-38)

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[4]	26 ^[5]		
Units: g/component				
arithmetic mean (standard deviation)	53.1 (± 5.7)	55.8 (± 5.9)		

Notes:

[4] - Number of test components produced: 301

[5] - Number of control components produced: 261

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence ^[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	-1.92

Notes:

[6] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component

Secondary: Post-production Hematocrit

End point title	Post-production Hematocrit
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

Post-production

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[7]	26 ^[8]		
Units: percentage				
arithmetic mean (standard deviation)	57.4 (± 2.0)	57.3 (± 2.9)		

Notes:

[7] - Number of test components produced: 389

[8] - Number of control components produced: 367

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence ^[9]
P-value	= 0.209
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.45

Notes:

[9] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component

Secondary: End of Storage Hematocrit

End point title	End of Storage Hematocrit
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

End of Storage (Day 35-38)

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[10]	26 ^[11]		
Units: percentage				
arithmetic mean (standard deviation)	60.4 (± 3.2)	60.9 (± 3.5)		

Notes:

[10] - Number of test components produced: 301

[11] - Number of control components produced: 261

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence ^[12]
P-value	= 0.149
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.12

Notes:

[12] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component

Secondary: End of Storage Hemolysis

End point title	End of Storage Hemolysis
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

End of Storage (Day 35-38)

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[13]	26 ^[14]		
Units: percentage				
arithmetic mean (standard deviation)	0.28 (± 0.12)	0.35 (± 0.16)		

Notes:

[13] - Number of test components produced: 301

[14] - Number of control components produced: 261

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001 ^[15]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	-0.04

Notes:

[15] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component.

Secondary: End of Storage Normalized ATP (BCW)

End point title	End of Storage Normalized ATP (BCW)
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

End of Storage (Day 35-38)

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[16]	26 ^[17]		
Units: µmol/g				
arithmetic mean (standard deviation)	1.66 (± 0.44)	1.29 (± 0.29)		

Notes:

[16] - Number of test components produced: 257

[17] - Number of control components produced: 222

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001 ^[18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.44

Notes:

[18] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component.

Secondary: End of Storage Normalized ATP (DRK)

End point title	End of Storage Normalized ATP (DRK)
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
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End point timeframe:

End of Storage (Day 35-38)

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[19]	26 ^[20]		
Units: µmol/g				
arithmetic mean (standard deviation)	2.8 (± 0.9)	2.4 (± 0.7)		

Notes:

[19] - Number of test components produced: 294

[20] - Number of control components produced: 262

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001 ^[21]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.59

Notes:

[21] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component.

Secondary: End of Storage Plasma Free Hemoglobin

End point title	End of Storage Plasma Free Hemoglobin
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End point description:

Secondary efficacy endpoints included the post-storage measurements of Hct, hemolysis, normalized ATP, plasma-free hemoglobin, and hemoglobin content. These endpoints were only collected from the non-transfused RBC components held until the end of storage (Day 35 to 38). Note that the hgb content at the end of storage was calculated by multiplying the hgb concentration (g/dL, measured at the end of storage) by the volume (mL, measured at post-production). The analysis was conducted using all RBC components available at the end of storage where:

- Proportion of T and C RBC components satisfying the EU guidelines for Hct, hemolysis, and hgb content were computed. The guidelines are: Between 50-70% for Hct; < 0.8% for hemolysis; and, ≥ 40 g/component for hgb content.
- Proportion of T and C RBC components that had normalized ATP levels >2 µmol/g (of Hgb) were computed.
- Proportion of T and C RBC components that had plasma-free hgb levels < 6 g/L (< 0.8% hemolysis) were computed.

End point type	Secondary
End point timeframe:	
End of Storage (Day 35-38)	

End point values	Test	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[22]	26 ^[23]		
Units: g/L				
arithmetic mean (standard deviation)	1.42 (± 0.64)	1.79 (± 0.88)		

Notes:

[22] - Number of test components produced: 263

[23] - Number of control components produced: 225

Statistical analyses

Statistical analysis title	ANCOVA model
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Statistical analysis description:

p-values were obtained from the full model where each covariate was included regardless of statistical significance; 95% CIs for the LS mean treatment difference (Test – Control) are based on a mixed effects ANCOVA model controlling for the treatment, gender, blood type, input hematocrit, and input volume.

Comparison groups	Test v Control
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001 ^[24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.23

Notes:

[24] - Equivalence between the Test and Control RBC components post production, prior to storage, was declared since the 95% CI for the mean treatment difference was well within the a-priori defined margins of -5 to 5 g/component.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from informed consent signature until study completion.

Adverse event reporting additional description:

Time of consent to the day of surgery (Day 0) - All AEs & SAEs (spontaneously reported to the attending physician)

Day 0 to Day 13 or discharge (whichever occurs first) - All AEs & SAEs (active surveillance by study staff)

Day 14 or day of discharge (whichever occurs first) to Day 90 - All SAEs (spontaneously reported to the attending physician)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Test RBC
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Reporting group description:

Treatment assessments were divided into an acute surgical care period starting at the day of surgery until 7 days post-surgery during which RBC (Test or Control) were administered and a post-surgical follow-up period of a minimum of 90 days to collect additional safety data.

Reporting group title	Control RBC
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Reporting group description:

Treatment assessments were divided into an acute surgical care period starting at the day of surgery until 7 days post-surgery during which RBC (Test or Control) were administered and a post-surgical follow-up period of a minimum of 90 days to collect additional safety data. The control article was conventional RBC components stored at 2°C to 6°C for up to 35 days post-donation and administered intravenously. Dose and schedule of RBC transfusions were determined by the treating physician.

Serious adverse events	Test RBC	Control RBC	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 25 (52.00%)	9 / 26 (34.62%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mantle cell lymphoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Hepatic rupture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iatrogenic injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplegia syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Hypertension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic fistula			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 25 (12.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (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	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 25 (12.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Test RBC	Control RBC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 25 (72.00%)	20 / 26 (76.92%)	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	6 / 25 (24.00%)	10 / 26 (38.46%)	
occurrences (all)	6	10	
Pneumothorax			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 25 (8.00%)	4 / 26 (15.38%)	
occurrences (all)	2	4	
Psychotic disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Coombs direct test			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Enterococcus test positive			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Coombs indirect test			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural			

complications			
Anaemia postoperative			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Facial bones fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Weaning failure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	6 / 25 (24.00%)	7 / 26 (26.92%)	
occurrences (all)	6	7	
Atrial tachycardia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Atrioventricular block			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 26 (0.00%) 0	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Subileus subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	0 / 26 (0.00%) 0	
Renal failure subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
renal failure acute subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Urinary tract obstruction subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Infections and infestations			

Anorectal infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Device related infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Endocarditis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2012	The updates to the CLI 00070 Protocol are as follows: - Provide the EUDRA CT Number for the Clinical Trial Application. - Add the competency in cardiovascular surgery at the clinical sites participating in this study. - Present the differences between the two blood centers in France and Germany in collection of whole blood and the overnight whole blood conditions prior to the production of RBC components. - Provide details on QP review and release of the RBC components prepared with the Second Generation S-303 Treatment Process. Also, provide details on the criteria for release of the RBC components into the clinical inventory. - Add clarification that Blood Center standard practices will be followed for matching the age of Test and Control RBC components. - Add details on the procedures for blinding Test and Control RBC units and differentiate between clinical site staff and Blood Center staff about blinding. - Provide details on the risks related to the user and patients and describe the procedures implemented to eliminate or reduce these potential risks. - Add two new exclusion criteria, to exclude patients with special requirements for gamma irradiated RBCs or removal of plasma and anyone with prior severe allergic transfusion reactions. - Provide description that effort will be made to match the age of Test and Control RBC components. Provide clarification that during the study, compatibility and phenotyping will be performed according to local standard practices and Good Transfusion Practices. - Include Direct and Indirect Antiglobulin Test at the end of study at Day 90 to detect any immunological changes after transfusion of study RBC units.
12 June 2012	The updates to the CLI 00070 Protocol are as follows: - Updated the protocol per PEI recommendations - Updated the protocol title match the protocol synopsis title that is more detailed in describing the protocol design and to reflect the new version. - Updated the abbreviations and definitions list to add ANCOVA – Analysis of Covariance, and ANOVA - Analysis of Variance - Updated Incubation time from 16 hours to 18 hours - Overall changes made for clarification purposes and also per the request from PEI several Quality Control measurements were added. - Investigational Plan- Inclusion Criteria: Add other criteria to be used by the Investigators along with the TRUST score to identify patients to include in the study. Add both genders to the inclusion criteria. Delete inclusion criteria "Must be willing to participate in the second 6MWT at 7 to 10 days after discharge". - Revise Six Minute Walk Test from "2-3 days prior to discharge" to "at the time of first ambulation". Update timing of Six Minute Walk Test and make reference to the study operations manual - Serum sample for S-303 antibody screening at pre-op (Day -7-0) removed as it is performed during screening (Day -30 - 0). - Revise the formatting to separate Exclusion criteria number 8 into 8, 9, and 10, then renumber the current numbers 9 and 10 to 11 and 12.
07 September 2012	The updates to the CLI 00070 Protocol are as follows: - Updated the incubation time for the preparation of test RBC components from 18 to 24 hours. - Updated the temperature for overnight incubation to 20-25°C. - Add the requirement to have an FDA Form 1572 included in the study files in addition to the MDA form

30 August 2013	The updates to the protocol include the following: -Updated to be more generic with regards to site and blood center, to avoid any future protocol amendments in the event additional sites or blood centers are added. For a multi-center study a Coordinating Investigator is required therefore the administrative structure was updated to reflect this. An external reviewer for telemetry will not be used for this study therefore this reference was deleted - Revised the text regarding the disposal of Test and Control components to clarify that study units must be retained until all study-specified assessments have been performed. The revised text provides clear instructions on timing of discarding of study components. To provide clarification to study sites on the timing and sequence for discarding component - Updated inclusion criteria regarding contraception and acceptable forms as well as the requirement for a negative pregnancy test for consistency. Remove the inclusion criteria for the requirement for a negative S-303 crossmatch at study entry - Added a new section titled, 'Additional Criteria to Satisfy Prior to Transfusion' to instruct the clinical site that patients must have a confirmed negative crossmatch for S-303 prior to receiving their first study transfusion - Added clarification that patients who receive a study transfusion but discontinue the study early must have their study assessments completed at the end of study. Clarification was made that only subjects who are exposed to study RBCs will be included in the total of 3 patients who demonstrate a confirmed positive crossmatch to S-303 RBCs. Add language around confirmed negative crossmatch requirement prior to study RBC transfusion and timing of follow-up - Changes made to reflect that quantitative safety data will be summarized descriptively, without formal statistical hypothesis testing - Updated the formula to identify site as the blood center and NOT the clinical site
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29498049>