Clinical trial results:
A Randomized Controlled Study to Evaluate Efficacy and Safety of S-303 Treated Red Blood Cells in Subjects with Thalassemia Major Requiring Chronic RBC Transfusion

Summary

EudraCT number	2012-002920-33
Trial protocol	IT GB
Global end of trial date	01 December 2017

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

Trial information

Trial identification

Sponsor protocol code	CLI 00076

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740531
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cerus Corporation
Sponsor organisation address	1220 Concord Avenue, Concord/CA, United States, 94520
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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	21 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2017
Global end of trial reached?	Yes
Global end of trial date	01 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy and safety of INTERCEPT treated RBCs (INTERCEPT RBC) in subjects who require chronic transfusion support due to thalassemia major (transfusion dependent thalassemia). This study was designed to support the licensure of the medical device, the INTERCEPT Blood System for Red Blood Cells (RBCs).

Protection of trial subjects:

The Informed Consent process complied with ICH Guidance for Industry – E6 Good Clinical Practice. 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:

Not Applicable

Evidence for comparator:

In a randomized crossover design each subject received 6 transfusion episodes of both INTERCEPT (Test) and untreated SAG-M (Control) RBC components. Each treatment period was initiated with 2 wash in RBC transfusion episodes followed by 4 efficacy RBC transfusion episodes. The Test product, INTERCEPT treated RBCs, was prepared from whole blood derived SAG-M RBC components which were stored in SAG-M following INTERCEPT treatment. Test components were administered by intravenous transfusion, and the dose (number of RBC) and dosing regimen for each subject was determined by the subject's treating physician. The hemoglobin content (g) of each RBC was determined after production at release into clinical inventory.The Reference product, conventional SAG-M RBC components derived from whole blood collections, were prepared according to the Blood Center's standard operating procedures and transferred to an identical storage container as the INTERCEPT treated RBC. The Reference product was administered by intravenous transfusion. The dose (number of RBC units) and dosing regimen for each subject was determined by the subject's treating physician. The hemoglobin content (g) of each RBCC was determined after production at release to clinical inventory.Subjects were transfused to maintain their pre-transfusion hemoglobin level above a target specified by the treating physician. After the final study RBC transfusion episode, each subject returned to their regular transfusion regimen with conventional (post-study) RBCs, as determined by their treating physician. Subjects were followed for safety over the next 2 conventional (post-study) RBC transfusion episodes or at least 45 days after the last study transfusion, whichever was greater; subject blood samples were tested for antibodies specific to INTERCEPT treated RBCs.

Actual start date of recruitment	30 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Turkey: 71
Worldwide total number of subjects	86
EEA total number of subjects	15

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)	5
Adolescents (12-17 years)	8
Adults (18-64 years)	73
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Stratified, blocked randomization scheme was generated by the CRO hosting the EDC system, with randomization being stratified by country. Patients were randomized to 1 of 2 treatment sequences (Test-Control or Control-Test) in 1:1 ratio and received either conventional RBCs or INTERCEPT RBCs during each assigned treatment period.

Pre-assignment

Screening details:

Subjects with Thalassemia Major were screened based on appropriate inclusion and exclusion criteria defined in the protocol.

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 Control RBCs to a Storage Container identical to the one used for Test RBCs. The labels for both components were identical.
Blood Center involved in processing, preparation, storage, cross-matching, and distribution of study RBCs were not blinded. Units were tracked in the Blood Center's management system.

Arms

Are arms mutually exclusive?	No
Arm title	Test RBCs

Arm description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as wash-in periods.
Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration.
Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints:
· Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis.
· Adverse events
· Transfusion reactions within 24 hours of a study transfusion
· Allo-immunization to RBC allo-antigens

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

Dosage and administration details:

Defined by patients need and determined by Hb/Hemaocrit requirements.

Arm title	Control RBCs

Arm description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as

wash-in periods. Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration. Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints: · Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis. · Adverse events · Transfusion reactions within 24 hours of a study transfusion · Allo-immunization to RBC allo-antigens less

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

Dosage and administration details:

Defined by patients need and determined by Hb/Hemaocrit requirements.

Number of subjects in period 1	Test RBCs	Control RBCs
Started	86	86
Completed	79	79
Not completed	7	7
Consent withdrawn by subject	1	1
Other	2	2
Post randomization ineligibility	4	4

Baseline characteristics

Reporting groups

Reporting group title	Test RBCs

Reporting group description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as wash-in periods.
Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration.
Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints:
· Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis.
· Adverse events
· Transfusion reactions within 24 hours of a study transfusion
· Allo-immunization to RBC allo-antigens

Reporting group title	Control RBCs

Reporting group description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as wash-in periods. Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration. Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints: · Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis. · Adverse events · Transfusion reactions within 24 hours of a study transfusion · Allo-immunization to RBC allo-antigens less

Reporting group values	Test RBCs	Control RBCs	Total
Number of subjects	86	86	86
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	5	5
Adolescents (12-17 years)	8	8	8
Adults (18-64 years)	73	73	73
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	48	48	48
Male	38	38	38

Subject analysis sets

Subject analysis set title	Test RBCs-ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis group included all randomized subjects who received at least one study RBC component with data for the primary efficacy analysis (n = 80)

Subject analysis set title	Control RBCs-ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis group included all randomized subjects who received at least one study RBC component with data for the primary efficacy analysis (n = 80)

Reporting group values	Test RBCs-ITT	Control RBCs-ITT	
Number of subjects	80	80	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	67	67	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	44		
Male	36		

End points

End points reporting groups

Reporting group title	Test RBCs

Reporting group description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as wash-in periods.
Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration.
Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints:
· Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis.
· Adverse events
· Transfusion reactions within 24 hours of a study transfusion
· Allo-immunization to RBC allo-antigens

Reporting group title	Control RBCs

Reporting group description:

Patients were randomized to one of two treatment sequences (Test-Control) or (Control-Test) and received Control RBCs or INTERCEPT RBCs during the assigned treatment period. Each patient served as his or her own control with two wash-in periods. Six transfusion cycles where by the first two served as wash-in periods. Efficacy:The efficacy endpoint was the average consumption of hemoglobin mass (g) normalized for subject body weight and duration. Safety: Safety assessments included monitoring study subjects for AEs and SAEs including the following safety endpoints: · Treatment-emergent antibody with confirmed specificity to INTERCEPT RBCs associated with clinically significant hemolysis. · Adverse events · Transfusion reactions within 24 hours of a study transfusion · Allo-immunization to RBC allo-antigens less

Subject analysis set title	Test RBCs-ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis group included all randomized subjects who received at least one study RBC component with data for the primary efficacy analysis (n = 80)

Subject analysis set title	Control RBCs-ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis group included all randomized subjects who received at least one study RBC component with data for the primary efficacy analysis (n = 80)

Primary: Average consumption of Hgb

End point title	Average consumption of Hgb

End point description:

The primary efficacy endpoint for this study was the mean treatment period (Test versus Control) averaged consumption of Hgb (g/kg/day) based on subject weight (kg) and duration (days) in each efficacy evaluation period.

End point type	Primary

End point timeframe:

Efficacy evaluation periods were the 4 efficacy transfusion episodes, following the first two “wash-in” transfusion episodes, from each treatment period.

End point values	Test RBCs	Control RBCs	Test RBCs-ITT	Control RBCs-ITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	80	80	80	80
Units: g/kg/day				
arithmetic mean (standard deviation)	0.113 (± 0.04)	0.111 (± 0.04)	0.113 (± 0.04)	0.111 (± 0.04)

Statistical analyses

Statistical analysis title	Paired T-test

Statistical analysis description:

The study included 80 subjects, in a cross over study design, who served as their own controls. The number of subjects below (160) is automatically populated by the system and does not reflect the correct number of subjects in the study design. The study design permitted use of a small non-inferiority margin of clinical relevance and included 80 subjects in each treatment period for a non-exclusive paired design to achieve 90% study power for the clinically relevant non-inferiority margin.

Comparison groups	Test RBCs-ITT v Control RBCs-ITT
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.373
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.005

Notes:

[1] - As described under the "Number of subjects included in analysis", a cross-over design was chosen for this study in which each subjects treated served as their own control and the true number of subjects included in the analysis is 80, not 160.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's were collected and recorded from the time of informed consent (or pediatric assent) until study participation completion (at the 2nd non-study transfusion episode or up to 45 days after the last study transfusion episode)

Adverse event reporting additional description:

Subjects were actively monitored for AEs during the transfusion episodes and until discharge from the transfusion clinic. Before admission to the transfusion clinic and after discharge, all AEs reported to the study staff/subject's treating physician were recorded; TEAEs were all AEs that occurred after exposure to at least one study transfusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Test period

Reporting group description:

Subjects enrolled in the study were randomized to receive 6 transfusion episodes of each treatment (Test and Control) in a double blind crossover design. The Test product, INTERCEPT treated RBCs, was prepared from whole blood derived SAG-M RBC components which were stored in SAG-M following INTERCEPT treatment. Test components were administered by intravenous transfusion, and the dose (number of RBC) and dosing regimen for each subject was determined by the subject's treating physician. The hemoglobin content (g) of each RBC was determined after production at release into clinical inventory

Reporting group title	Control Period

Reporting group description:

Subjects enrolled in the study were randomized to receive 6 transfusion episodes of each treatment (Test and Control) in a double blind crossover design. The Reference product, conventional SAG-M RBC components derived from whole blood collections were prepared according to the Blood Center's standard operating procedures and transferred to an identical storage container as the INTERCEPT treated RBC. The Reference product was administered by intravenous transfusion. The dose (number of RBC units) and dosing regimen for each subject was determined by the subject's treating physician. The hemoglobin content (g) of each RBCC was determined after production at release to clinical inventory.

Serious adverse events	Test period	Control Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 81 (3.70%)	5 / 80 (6.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Mononeuropathy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Test period	Control Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 81 (67.90%)	57 / 80 (71.25%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Cyst removal			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Labial frenectomy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Plastic surgery			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Tooth extraction			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	

Pyrexia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 81 (4.94%)	4 / 80 (5.00%)	
occurrences (all)	4	5	
Oropharyngeal pain			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	
occurrences (all)	2	2	
Productive cough			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Pulmonary hypertension			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 81 (0.00%)	3 / 80 (3.75%)	
occurrences (all)	0	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)		
occurrences (all)	0	1		
Blood glucose increased				
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)		
occurrences (all)	0	1		
Body temperature increased				
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)		
occurrences (all)	1	0		
False positive investigation result				
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)		
occurrences (all)	0	1		
Haemoglobin urine present				
subjects affected / exposed	7 / 81 (8.64%)	10 / 80 (12.50%)		
occurrences (all)	7	10		
Platelet count decreased				
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)		
occurrences (all)	0	1		
Red blood cells urine positive				
subjects affected / exposed	9 / 81 (11.11%)	5 / 80 (6.25%)		
occurrences (all)	11	5		
Ultrasound kidney abnormal				
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)		
occurrences (all)	0	1		
Urine protein/creatinine ratio abnormal				
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)		
occurrences (all)	0	3		
Urine protein/creatinine ratio increased				
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)		
occurrences (all)	1	0		
Weight decreased				
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)		
occurrences (all)	1	0		
Weight increased				

subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	1	2	
Meniscus injury			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Urethral stricture postoperative			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Extrasystoles			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	3	0	
Sinus tachycardia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Headache			
subjects affected / exposed	3 / 81 (3.70%)	4 / 80 (5.00%)	
occurrences (all)	3	4	
Syncope			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 81 (6.17%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Extramedullary haemopoiesis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Chalazion			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Eye pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	
occurrences (all)	2	3	
aphthous stomalitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 81 (3.70%)	0 / 80 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Food poisoning			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Oral pruritus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	3 / 81 (3.70%)	4 / 80 (5.00%)	
occurrences (all)	4	4	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Hepatitis chronic active			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Glycosuria			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	5 / 81 (6.17%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Haemoglobinuria			
subjects affected / exposed	10 / 81 (12.35%)	9 / 80 (11.25%)	
occurrences (all)	11	10	
Hyperoxaluria			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	3 / 81 (3.70%)	1 / 80 (1.25%)	
occurrences (all)	3	1	
Proteinuria			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Strangury			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	3 / 81 (3.70%)	2 / 80 (2.50%)	
occurrences (all)	3	2	
Bone pain			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Lordosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Osteoporosis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Tendonitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Acute sinusitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	2	
Atypical pneumonia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences (all)	1	1	

Cystitis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Gastroenteritis			
subjects affected / exposed	2 / 81 (2.47%)	3 / 80 (3.75%)	
occurrences (all)	2	4	
Gastroenteritis viral			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Gingivitis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Herpes simplex			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	3 / 81 (3.70%)	1 / 80 (1.25%)	
occurrences (all)	3	1	
Localised infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	

Postoperative wound infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	3 / 81 (3.70%)	3 / 80 (3.75%)	
occurrences (all)	3	3	
Sinusitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 81 (4.94%)	9 / 80 (11.25%)	
occurrences (all)	4	9	
Urinary tract infection			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	
occurrences (all)	2	2	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Glucose tolerance impaired			
subjects affected / exposed	0 / 81 (0.00%)	3 / 80 (3.75%)	
occurrences (all)	0	3	
Impaired fasting glucose			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2012	The updates to the CLI 00076 protocol include: -The description of Control RBC component, Input RBC, S-303 treated RBC, Investigational product were modified ("leukocyte-depleted") to conform to standard operating procedures at the study Blood Centers; EDQM uses depleted, not reduced. -The donation and preparation of study RBC was modified to conform to the standard operating procedures at the study Blood Centers. -The information with regards to whole blood collection and processing was modified to allow the blood centers to use their established procedures and available disposables to process leukocyte depleted RBC in additive solution. -Updated Subject Exclusion Criteria: Added definition to splenic enlargement to accurately define splenomegaly by ultrasound. Splenomegaly is important to identify because it can affect the primary efficacy endpoint. Added an exclusion, the purpose of this change is to assure, to the extent possible, that any change in the number of RBC units transfused is due to the performance of the Investigational Product and not simply to growth of the patient. - Updated the Subject Exclusion Criteria to allow for better representation of the patient population currently treated for thalassemia major. - Updated Subject Exclusion Criteria for additional clarification per Investigator's recommendation. - Updated the verbiage for the methods and timing of Efficacy Parameters for additional clarification and in accordance with the Investigator's SOPs and requirements. - Additional updates to ensure per Investigator's recommendations and ensure consistency.
27 February 2014	The updates to the CLI 00076 protocol include: - Updated the Medical Monitor. - Modification made to improve the protocol in accordance with Ministry of Health observations: Updates to clarify that the Blood Centers operate according to Italian regulations. Removed reference to "licensed" Blood Centers. Clarified description of Qualified Person (QP). Clarified that the RBC components are collected according to applicable Italian regulation and the Test and Control RBCs will meet the Council of Europe Guidelines (2010). Evaluation and Disposition of Red Blood Cells at the Blood Centers – clarification added that RBCs are tracked by donation number using the existing electronic data management system. Storage and Disposition of Red Blood Cells at Clinical Sites - Added details about the maximum age of RBC components for transfusion to subjects with Thalassemia. Detection and Confirmation of Antibody Specific to S-303 Treated RBC - Added details about secondary screening panel and clarified the scoring and classification of the test results. - Administration of Study Treatments - Text added to provide method for determining amount of hemoglobin transfused. - Subject Participation - Added safety follow-up for 2 non-study transfusions and clarified end of subject participation in the study. - New Inclusion Criteria added and updated exclusion criteria to clarify requirements for Female subjects. Updated the Exclusion Criteria to add information about participation in another study. - Treatment Plan Updated - Added extended safety follow-up period and modified end of subject participation to improve protocol clarity and study conduct. - Study Assessments table updated for consistency with the study requirements.

01 May 2015	The updates to the CLI 00076 protocol include: -Increased number of clinical study sites, and updated the Clinical Project Manager. - Updated: Timing of whole blood processing by centrifugation to within 24 hours of collection. - Clarified the non-inferiority margin of the primary efficacy endpoint and deleted the secondary efficacy endpoints. Hgb increment 1hr post-transfusion and % Proportional decline in post transfusion hgb level per day (%/day). Clarified the study randomization scheme and process. - Updated: Subjects will be followed for safety for 2 non-study RBC transfusion episodes after the last study transfusion or 45 days, whichever is greater. Deleted: References to a separate biotin study. - Modified Inclusion Criteria: Subjects ≥4 years old are eligible (previously ≥10 years old), negative DAT modified as an exclusion requirement, requirement for stable iron chelation regimen removed, removed subject available for 1-hr post transfusion blood sample, and added pediatric assent, if applicable. - Updated the Exclusion Criteria: Clarify and modify eligibility of subjects with positive DAT, subjects at risk for cardiac decompensation, subjects with G-6DR deficiency requiring medications known to adversely affect RBC viability, algorithm to exclude some DAT positive subjects, concurrent chemotherapy for cancer, and inability to comply with the protocol. - Clarified withdrawal of subjects treated with medication demonstrated to have caused hemolysis while on study and allow for replacement of subjects who withdraw prior to being transfused. -Updated screening assessments, to allow the inclusion of a subset of DAT positive subjects and improve the current enrollment rate. Added details for evaluation of positive DAT reactions and development of positive DAT during the trial. -Updated Subject Inclusion Criteria: Updated the minimum age to ≥11 years. Response to ANSM letter 16 Jul 2014. Updated withdrawal criteria: added withdrawal of subjects.

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/31148155