Clinical trial results:
Eculizumab in Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (ECUSTEC): A Randomised, Double-Blind, Placebo-Controlled Trial

Summary

EudraCT number	2016-000997-39
Trial protocol	GB
Global end of trial date	01 July 2021

Results information

Result version number	v1 (current)
This version publication date	25 November 2021
First version publication date	25 November 2021

Trial information

Trial identification

Sponsor protocol code	7837

Additional study identifiers

ISRCTN number	ISRCTN89553116
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Ref No: 16/NE/0325, ISRCTN: 89553116, MHRA CTA: 17136/0282/001-0001

Notes:

Sponsors

Sponsor organisation name	Newcastle upon Tyne Hospitals
Sponsor organisation address	Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN, Newcastle, United Kingdom,
Public contact	Sean Scott, Newcastle upon Tyne Hospitals NHS Foundation Trust, +44 01912825969, Tnu-tr.sponsormanagement@nhs.net
Scientific contact	Sean Scott, Newcastle upon Tyne Hospitals NHS Foundation Trust, +44 01912825969, Tnu-tr.sponsormanagement@nhs.net

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	01 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether the severity of Shiga-toxin producing Escherichia Coli Haemolytic Syndrome (STEC HUS) is less in patients who receive eculizumab, compared to those given placebo.

Protection of trial subjects:

All sites were provided with the ECUSTEC protocol that contained specific instruction relating to inclusion/exclusion criteria and trial patient safety. There was clear instruction relating to trial intevention safety and considerations detailed within the protocol. ECUSTEC had a Data Monitoring Committee to monitor patient safety throughout the trial.

Background therapy:

The use of Ecu for the treatment of severe STEC HUS is increasing internationally, with no objective evidence of efficacy or safety in children or adults, and at a huge cost to the NHS and other health services. It is therefore important that the efficacy and safety of Ecu in STEC HUS is properly evaluated in a prospective randomised controlled trial.

In our study, ECUSTEC, we assesed giving Ecu early in the disease course, have a wider objective, to consider reduction in the overall disease severity, rather than just renal disease severity, have a double-blind design and are examining fewer doses of Ecu. ECUSTEC also provide a health economic analysis to allow further assessment of the role of Ecu in managing STEC HUS in children.

Evidence for comparator:

Eculizumab in Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (ECUSTEC): A Randomised, Double-Blind, Placebo-Controlled Trial. Recruited patients will receive either Eculizumab, formulation 10mg/ml concentrate for solution for infusion (30ml vial) or placebo (Sodium chloride 0.9%) formulation intravenous infusion bags. Ecu increases children’s susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

To reduce the risk of meningococcal disease, all ECUSTEC trial participants are given:
1. Antibiotic prophylaxis
2. Vaccination against meningococcus
3. Information on the early features of meningococcal diseases

Patients will be followed-up for the duration of the treatment.

Actual start date of recruitment	11 August 2017
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	United Kingdom: 36

Worldwide total number of subjects	36
EEA total number of subjects	0

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)	7
Children (2-11 years)	26
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant was randomised on the 11th August 2017 and the last patient was randomised on the 7th February 2020. A total of 36 participants were randomised into ECUSTEC. Patients were equally recruited with 17 patient in the Eculizumab arm and 19 participants in the placebo arm.

Pre-assignment

Screening details:

A total of 108 participants were identified, of these identified 87 participants were approach and 36 were randomised.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Assessor, Subject

Blinding implementation details:

All site personnel were blinded apart from those responsible for preparing the IMP (e.g. pharmacy), who made sure that no other person, had access to the study drugs and pharmacy documentation, and remained independent to the treatment of all trial participants. After randomisation, the unblinded staff received the treatment allocation electronically from BCTU. The unblinded staff prepared an intravenous (IV) infusion bag containing either sodium chloride 0.9% with Ecu o placebo (NaCl, 0.9%)

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

To reduce the risk of meningococcal disease, all ECUSTEC trial participants are given:
1. Antibiotic prophylaxis
2. Vaccination against meningococcus
3. Information on the early features of meningococcal disease

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Arm title	Placebo

Arm description:

Placebo, Sodium chloride 0.9%

Arm type	Placebo
Investigational medicinal product name	Placebo, Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details:

5 to <10kg-60 ml of 0.9% Saline
10 to <20 Kg-120 ml of 0.9% Saline
20 to <40 kg-120 ml of 0.9% Saline
≥40kg -180 ml of 0.9% Saline

Number of subjects in period 1	Eculizumab	Placebo
Started	17	19
Completed	17	19

Period 2

Period 2 title	30 days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All site personnel were blinded apart from those responsible for preparing the IMP (e.g. pharmacy), who made sure that no other person, had access to the study drugs and pharmacy documentation, and remained independent to the treatment of all trial participants. After randomisation, the unblinded staff received the treatment allocation electronically from BCTU. The unblinded staff prepared an intravenous (IV) infusion bag containing either sodium chloride 0.9% with Ecu o placebo (NaCl, 0.9%)]

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

Randomised, parallel group, double blind, placebo-controlled trial

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Arm title	Placebo

Arm description:

NaCL 0.9% saline infusion

Arm type	Placebo
Investigational medicinal product name	NaCl 0.9% saline infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

0.9% saline

Investigational medicinal product name	Placebo, Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

5 to <10kg-60 ml of 0.9% Saline
10 to <20 Kg-120 ml of 0.9% Saline
20 to <40 kg-120 ml of 0.9% Saline
≥40kg -180 ml of 0.9% Saline

Number of subjects in period 2	Eculizumab	Placebo
Started	17	19
Completed	16	19
Not completed	1	0
Adverse event, serious fatal	1	-

Period 3

Period 3 title	60 days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All site personnel were blinded apart from those responsible for preparing the IMP (e.g. pharmacy), who made sure that no other person, had access to the study drugs and pharmacy documentation, and remained independent to the treatment of all trial participants. After randomisation, the unblinded staff

received the treatment allocation electronically from BCTU. The unblinded staff prepared an intravenous (IV) infusion bag containing either sodium chloride 0.9% with Ecu o placebo (NaCl, 0.9%).

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Arm title	Placebo

Arm description:

Placebo, Sodium chloride 0.9%

Arm type	Placebo
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Investigational medicinal product name	Placebo, Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details:

5 to <10kg-60 ml of 0.9% Saline
10 to <20 Kg-120 ml of 0.9% Saline
20 to <40 kg-120 ml of 0.9% Saline
≥40kg -180 ml of 0.9% Saline

Number of subjects in period 3	Eculizumab	Placebo
Started	16	19
Completed	15	19
Not completed	1	0
Consent withdrawn by subject	1	-

Period 4

Period 4 title	26 Weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All site personnel were blinded apart from those responsible for preparing the IMP (e.g. pharmacy), who made sure that no other person, had access to the study drugs and pharmacy documentation, and remained independent to the treatment of all trial participants. After randomisation, the unblinded staff received the treatment allocation electronically from BCTU. The unblinded staff prepared an intravenous (IV) infusion bag containing either sodium chloride 0.9% with Ecu o placebo (NaCl, 0.9%)

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children’s susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Arm title	Placebo

Arm description:

Placebo, Sodium chloride 0.9%

Arm type	Placebo

Investigational medicinal product name	Placebo, Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details:

5 to <10kg-60 ml of 0.9% Saline
10 to <20 Kg-120 ml of 0.9% Saline
20 to <40 kg-120 ml of 0.9% Saline
≥40kg -180 ml of 0.9% Saline

Number of subjects in period 4	Eculizumab	Placebo
Started	15	19
Completed	15	19

Period 5

Period 5 title	52 Weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All site personnel were blinded apart from those responsible for preparing the IMP (e.g. pharmacy), who made sure that no other person, had access to the study drugs and pharmacy documentation, and remained independent to the treatment of all trial participants. After randomisation, the unblinded staff received the treatment allocation electronically from BCTU. The unblinded staff prepared an intravenous (IV) infusion bag containing either sodium chloride 0.9% with Ecu o placebo (NaCl, 0.9%)

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

The dose of Ecu and volume given will be dependent on the individual participant's bodyweight.
5 to <10kg-Dose of Eculizumab 300mg
10 to <20 Kg-Dose of Eculizumab 600mg
20 to <40 kg-Dose of Eculizumab 600 mg
≥40kg -Dose of Eculizumab 900mg

Arm title	Placebo

Arm description:

Placebo, Sodium chloride 0.9%

Arm type	Placebo
Investigational medicinal product name	Placebo, Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details:

5 to <10kg-60 ml of 0.9% Saline
10 to <20 Kg-120 ml of 0.9% Saline
20 to <40 kg-120 ml of 0.9% Saline
≥40kg -180 ml of 0.9% Saline

Number of subjects in period 5	Eculizumab	Placebo
Started	15	19
Completed	15	19

Baseline characteristics

Reporting groups

Reporting group title	Eculizumab

Reporting group description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

To reduce the risk of meningococcal disease, all ECUSTEC trial participants are given:
1. Antibiotic prophylaxis
2. Vaccination against meningococcus
3. Information on the early features of meningococcal disease

Reporting group title	Placebo

Reporting group description:

Placebo, Sodium chloride 0.9%
Brand: any brand with marketing authorisation within EEA
Formulation: Intravenous Infusion bags

Reporting group values	Eculizumab	Placebo	Total
Number of subjects	17	19	36
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	4	7
Children (2-11 years)	13	13	26
12 years-17 years	1	2	3
Gender categorical Units: Subjects			
Female	10	10	20
Male	7	9	16
pRIFLE category Units: Subjects			
Injury	2	1	3
Failure	15	18	33
Volume of 0.9% saline (ml/Kg) Units: Subjects			
<=20	13	13	26
>20	4	6	10

End points

End points reporting groups

Reporting group title	Eculizumab

Reporting group description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

To reduce the risk of meningococcal disease, all ECUSTEC trial participants are given:
1. Antibiotic prophylaxis
2. Vaccination against meningococcus
3. Information on the early features of meningococcal disease

Reporting group title	Placebo

Reporting group description:

Placebo, Sodium chloride 0.9%
Brand: any brand with marketing authorisation within EEA
Formulation: Intravenous Infusion bags

Reporting group title	Eculizumab

Reporting group description:

Randomised, parallel group, double blind, placebo-controlled trial

Reporting group title	Placebo

Reporting group description:

NaCL 0.9% saline infusion

Reporting group title	Eculizumab

Reporting group description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Reporting group title	Placebo

Reporting group description:

Placebo, Sodium chloride 0.9%

Reporting group title	Eculizumab

Reporting group description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Reporting group title	Placebo

Reporting group description:

Placebo, Sodium chloride 0.9%

Reporting group title	Eculizumab

Reporting group description:

IMPs-Eculizumab Brand: Soliris
Formulation: 10mg/ml Concentrate for solution for infusion (30ml vial). Ecu increases children's susceptibility to meningococcal disease, particularly due to uncommon serogroups (e.g. Y, W and X), although meningococcal disease due to any serogroup (including B or C) may occur.

Reporting group title	Placebo

Reporting group description:
Placebo, Sodium chloride 0.9%

Primary: Clinical severity score (CSS)

End point title	Clinical severity score (CSS)

End point description:

End point type	Primary

End point timeframe:
Day 60

End point values	Eculizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Score				
arithmetic mean (standard deviation)	11.5 (± 8.4)	14.6 (± 7.7)		

Statistical analyses

Statistical analysis title	Mean CSS comparison
Comparison groups	Placebo v Eculizumab
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	2.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

If an AE meets the criteria of a SAE for ECUSTEC and occurs within 90 days of the first dose of meningococcal vaccination or prophylactic antibiotic (whichever occurs first) it is reported to the trial office.

Adverse event reporting additional description:

Events identified as SAEs require completion of an SAE form. A trial-specific SAE form is forwarded to BCTU within 24 hours of the research staff becoming aware of the event.
Events categorised as Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the Main REC and MHRA within the required timeframes.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Eculizumab
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Eculizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 17 (29.41%)	1 / 19 (5.26%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Dyalisis	Additional description: Serum amylase increased haemolytic uremic syndrome, general anaesthetic for dialysis central line		
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury	Additional description: Death due to severe brain injury		
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Horner syndrome			

subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemic		
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Prologed NAT feeding post discharge			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
rash	Additional description: Rash to arm and legs		
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eculizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	2 / 19 (10.53%)	
Immune system disorders			
Infection	Additional description: The development of any significal infections (grade 3 or above)		
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
STEC	Additional description: The presence of STEC in a stool sample which is collected at day 30		
subjects affected / exposed	3 / 17 (17.65%)	1 / 19 (5.26%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2016	Version 2.0 -Changes to the initial protocol requested by the MHRA including information about contraception, pregnancy testing, more frequent CNS examinations and SUSAR reporting.
01 April 2017	Version 3.0-Changes to incorporate those requested by REC for Version 1.0 7th September 2016 and MHRA requested changes for Version 2.0 12th December 2016 reviewed the updated stool SOP 016. Additional inclusion criteria and wording of an exclusion criteria. Further detail added regarding confirmation of vaccinations. Amendments to the assessments schedule, data collection, samples guidance and AE reporting sections. Other minor changes.
18 January 2018	Version 4.0-The treatment window has been extended by 12 hours due to the operational difficulty of treating patients. Other minor changes.
24 June 2019	Version 5.0- The wording for inclusion criteria 4 has been amended to include "OR Passage of blood per rectum within 14 days prior to diagnosis of HUS". Also refined household contact to: Stool culture or shiga toxin polymerase chain reaction (PCR) or STEC serology result indicating STEC in a close contact (household or institutional). Other changes include an update to the UK Data Protection Act 2018, re-wording of events that do not require expedited reporting and other minor changes.
26 May 2020	Version 6.0- The treatment window has been extended by 24 hours due to the operational difficulty of treating patients within the current window. Other minor changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 March 2020	COVID 19 Pandemic. Notification of suspension of recruitment. Due to the COVID-19 pandemic rapidly evolving situation within Trusts in the UK in March 2020, the strain that it was putting on our clinical collaborators, and current government adviced to stop unnecessary contact with other people. The trial team and trial steering committee chair agreed to suspend temporarily the ECUSTEC trial. The ECUSTEC trial team did not have confidence that children recruited in the remaining sites would have been able to attend their follow-up visits, particularly the crucial day 60 visit to collect the primary outcome data. For this reason, we proposed to suspend recruitment for an initial two month period. The situation was reviewed after the two month suspension and a further extension suspension was implemented.	-

Notes:

Limitations and caveats

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

None reported.

Notes: