



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

Dear Consultant Paediatric Neurologist,

Re: ECUSTEC Day 60 Central Nervous System Assessment – guidance for Paediatric Neurologists

Thank you for your willingness to be a part of the ECUSTEC trial. The primary outcome measure is a multi-domain clinical severity score that captures the severity of renal and extra-renal events as a consequence of Shiga-Toxin E. Coli Haemolytic Uraemic Syndrome (STEC HUS) (Appendix 1). It is assigned after the Day 60 assessment.

The CNS domain score is shown here:

| CNS score (assign the highest score that applies) | |
|---|----|
| Altered consciousness (Agitation or irritability or hallucinations or confusion or excessive drowsiness) | 2 |
| Single seizure | 4 |
| Two or more seizures 24 hrs apart* | 6 |
| Transient focal neurological defect (>24 hrs** but <1 week) | 7 |
| Persistent focal neurological defect (present at day 60 and persistent for more than 1 week) | 10 |
| Persistent global (≥ 2 brain functions - vision/hearing/cognitive/motor/sensory/memory) neurological defect at day 60 | 15 |

* Multiple seizures occurring within a 24 hr period considered part of the same event

**Todd's paresis following a seizure should resolve within 24 hrs

If any of the following features are present during the acute illness, the research team at the recruiting hospital will arrange CNS assessment as part of the Day 60 assessment:

| CNS features during acute illness that indicate the need for the Day 60 CNS assessment |
|--|
| Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness) |
| Seizure/s |
| Focal or global neurological defect of any duration |

The Day 60 CNS assessment will comprise:

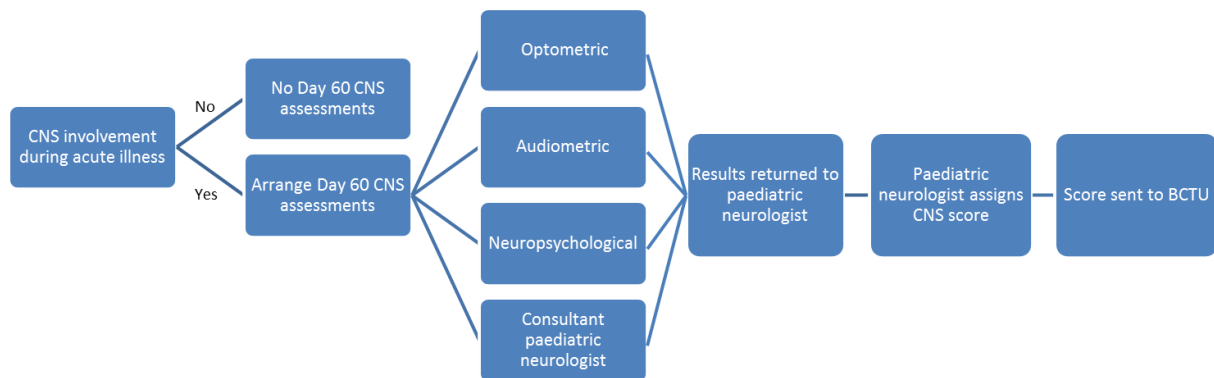
1. Structured examination by Consultant Paediatric Neurologist
2. Visual assessment by an optometrist and ophthalmologist
3. Hearing assessment by an audiologist

4. Neuropsychology assessment (parental completion of the Adaptive Behaviour Assessment System Third Edition (ABAS-3) form) supervised by a neuropsychologist

Worksheets for these assessments are contained within the site file, and an example of each is enclosed with this guidance (Appendix 2). These are designed to capture new features of CNS disease that since the onset of STEC HUS. Any pre-existing abnormalities should not be recorded.

Once the Day 60 CNS assessments are complete, we would be grateful if you would review the data from the worksheets and assign the appropriate CNS score which will be sent to BCTU via the Day 60 Case Report Form (CRF). This will be added to the scores from the other domains to complete the primary outcome measure.

This process is summarised in the diagram below:



Once again, many thanks for your support for the ECUSTEC trial. If you have any questions please do not hesitate to contact:

Principal Investigator:

BCTU: Emma Barsoum, Senior Trial Coordinator Tel. 0121 415 9132 or email ecustec@trials.bham.ac.uk

Chief Investigator: Dr Sally Johnson Tel. 0121 282 4917 or email Sally.Johnson@nuth.nhs.uk

Yours sincerely

Dr Sally Johnson

Chief Investigator ECUSTEC Trial

Appendix 1: Clinical Severity Score (primary outcome measure)

| | | |
|--------------------------|---|----|
| Renal | Lowest eGFR >50 | 1 |
| | Lowest eGFR 26-50, no oligoanuria* | 2 |
| | Lowest eGFR ≤ 25, no oligoanuria* | 3 |
| | Oligoanuria* but no dialysis (or renal replacement therapy, RRT) required | 4 |
| | Dialysis/RRT <48 hours | 5 |
| | Dialysis/RRT 2 days | 6 |
| | Dialysis/RRT 3 days | 7 |
| | Dialysis/RRT 4 days | 8 |
| | Dialysis/RRT 5 days | 9 |
| | Dialysis/RRT 6 days | 10 |
| | Dialysis/RRT 7 days | 11 |
| | Dialysis/RRT 8 days | 12 |
| | Dialysis/RRT 9 days | 13 |
| | Dialysis/RRT 10 days | 14 |
| | Dialysis/RRT 11 days | 15 |
| | Dialysis/RRT 12 to 13 days | 16 |
| | Dialysis/RRT 14 to 17 days | 17 |
| | Dialysis/RRT 18 to 20 days | 18 |
| | Dialysis/RRT 21 to 27 days | 19 |
| | Dialysis/RRT 28 to 34 days | 20 |
| | Dialysis/RRT 35 to 41 days | 21 |
| | Dialysis/RRT 42 to 48 days | 22 |
| | Dialysis/RRT 49 to 55 days | 23 |
| | Dialysis/RRT >55 days | 24 |
| CNS | No obvious CNS involvement | 0 |
| | Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness) | 2 |
| | Single seizure | 4 |
| | Two or more seizures 24 hrs apart** | 6 |
| | Transient focal neurological defect (>24 hrs*** but <1 week) | 7 |
| | Persistent focal neurological defect (present at day 60 and persistent for more than 1 week) | 10 |
| | Persistent global (≥ 2 brain functions - vision/hearing/cognitive/motor/sensory/memory) neurological defect at day 60 | 15 |
| Pancreas | No clinical or biochemical evidence pancreatitis | 0 |
| | Raised amylase and/or lipase† without clinical symptoms/signs | 2 |
| | Hyperglycaemia without insulin requirement | 6 |
| | Pancreatitis with sequelae (laparotomy, parenteral nutrition††, insulin required) | 8 |
| | Chronic sequelae of pancreatitis at day 60 (parenteral nutrition††, insulin, other) | 10 |
| Gastro-intestinal | No abdominal surgery required (except related to peritoneal dialysis catheter) | 0 |
| | Laparoscopy/laparotomy required for abdominal symptoms | 5 |
| | Intestinal perforation AND/OR bowel resection required | 8 |

| | | |
|----------------|---|----|
| | Stoma formation | 10 |
| Cardiac | No cardiac involvement (normal CVS examination - except hypertension/volume overload) | 0 |
| | Cardiac failure confirmed by ECHO††† (impaired systolic ventricular function or chamber enlargement or valve regurgitation) | 4 |
| | Cardiac failure confirmed by ECHO with dilated cardiomyopathy | 6 |
| | Myocardial infarction (on standard ECG +/- troponin +/- ECHO evidence) | 10 |

*oligoanuria defined as urine output <0.5ml/kg/hr for 12 hours

** Multiple seizures occurring within a 24 hr period considered part of the same event

***Todd's paresis following a seizure should resolve within 24 hrs

† lipase measurement not mandatory, however if measured and found to be elevated this would count

†† only if parenteral nutrition is required because of pancreatitis, not for other indications

††† ECHO only mandatory if clinical signs of cardiac failure or myocardial infarction

Within each domain, highest score at any point in first 60 days is recorded and score for each domain is added together to give total clinical severity score.

Abbreviations: eGFR estimated glomerular filtration rate; RRT renal replacement therapy; CNS central nervous system; CVS cardiovascular system; ECHO echocardiogram.

Appendix 2: ECUSTEC Day 60 Assessment CNS Worksheets

ECUSTEC Audiometric Examination Worksheet

| | | | | | | |
|-----------------------|--|--|--|--|--|--|
| Hospital name: | | | | | | |
| Trial number: | <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> | | | | | |
| | | | | | | |
| Date of Birth: | ___/___/___ | | | | | |

Please complete this worksheet for the day 60 assessment visit if the patient experienced CNS features during the acute disease (STEC HUS). Once completed, the paediatric neurologist responsible will use the information on the worksheet as Source Data from which to assign a CNS score for the ECUSTEC trial.

Audiometry using age/ability appropriate method

| | | | |
|------------------|------------------------------|--------------------------|---|
| Test used | | | |
| | Visual reinforced audiometry | <input type="checkbox"/> | |
| | Play audiometry | <input type="checkbox"/> | |
| | Standard audiometry | <input type="checkbox"/> | |
| | Other | <input type="checkbox"/> | state which |
| Result Left Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> Not possible <input type="checkbox"/> |
| Result Right Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> Not possible <input type="checkbox"/> |

Tympanometry

| | | | | |
|------------------|--------|--------------------------|-----------------------------------|---------------------------------------|
| Result Left Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Result Right Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |

Bone conduction

| | | | | |
|------------------|--------|--------------------------|-----------------------------------|---------------------------------------|
| Result Left Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Result Right Ear | Normal | <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |

Summary

| | | |
|---|--------------------------|--|
| Does this child have sensorineural hearing loss? | | |
| Yes | <input type="checkbox"/> | No <input type="checkbox"/> Unable to comment <input type="checkbox"/> |
| If yes, in your opinion (from parental reports and any available pre-morbid records) has this occurred since diagnosis of STEC HUS? | | |
| Yes | <input type="checkbox"/> | No <input type="checkbox"/> Unable to comment <input type="checkbox"/> |

Supporting comments

ECUSTEC Source Data: this worksheet is to be filed in the ECUSTEC Site File and a copy should be added to the patient medical notes.

ECUSTEC Central Nervous System (CNS) Assessment Worksheet

| | | | | | | |
|-----------------------|---|---|--|---|--|--|
| Hospital name: | | | | | | |
| Trial number: | <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> | | | | | |
| | | | | | | |
| Date of Birth: | <table style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; border-bottom: 1px solid black;"></td> <td style="width: 20px; border-bottom: 1px solid black;"></td> <td style="width: 10px; border-bottom: 1px solid black; text-align: center;">/</td> <td style="width: 20px; border-bottom: 1px solid black;"></td> <td style="width: 20px; border-bottom: 1px solid black;"></td> </tr> </table> | | | / | | |
| | | / | | | | |

Please complete this worksheet for the day 60 assessment visit if the patient experienced CNS features during the acute disease (STEC HUS). Once completed, the paediatric neurologist responsible will use the information on the worksheet as Source Data from which to assign a CNS score for the ECUSTEC trial.

ECUSTEC CNS Assessment*

| Level of consciousness / alertness | | | |
|---|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details if abnormal | | | |

| Cranial nerves | | | |
|-----------------------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details if abnormal | | | |

| Tone | | | |
|---------------------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details if abnormal | | | |

| Abnormalities of movement | | | |
|----------------------------------|--|---|---------------------------------------|
| Result | No abnormal movements <input type="checkbox"/> | Abnormal movements <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details of abnormal movements | | | |

| |
|--------------------------------------|
| Abnormalities of balance/gait |
|--------------------------------------|

| | | | |
|----------------------------------|---|---|---------------------------------------|
| Result | Normal balance/gait <input type="checkbox"/> | Abnormal balance/gait <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details of abnormal balance/gait | | | |

| | | | |
|---------------------|--------------------------------------|--|---------------------------------------|
| Weakness | | | |
| Result | No weakness <input type="checkbox"/> | Weakness present <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details of weakness | | | |

| | | | |
|-----------------------|---|--|---------------------------------------|
| Neuropathy | | | |
| Result | No neuropathy <input type="checkbox"/> | Evidence of neuropathy <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details of neuropathy | | | |

| | | | |
|--|---|---------------------------------------|---------------------------------------|
| New epileptic seizures (since onset STEC HUS) | | | |
| Result | No new seizures <input type="checkbox"/> | New seizures <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| Details of seizures | | | |

| | | | |
|--|-----------------------------|--|--|
| Summary | | | |
| Does this child have a normal neurological examination? | | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> | |
| If no, in your opinion (from parental reports and any available pre-morbid records) has this occurred since onset of STEC HUS? | | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> | |
| | | | |

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*Examination should include the following:

- Level of consciousness / alertness
- Abnormalities of cranial nerves
 - Single
 - Multiple
- Abnormalities of tone
 - Hypotonia
 - Axial
 - Post-axial
 - Hypertonia
 - Spastic or dystonic
 - Generalised or focal
 - Arms v legs
 - Trunk v limbs
 - Head lag/drop
- Abnormalities of movement
 - Tremor
 - Location
 - Rest v Action v Postural
 - Symmetrical
 - Myoclonus
 - Choreoathetosis
 - Location
 - Frequency
- Abnormalities of balance/gait
 - Cerebellar ataxia
 - Upper limb dysmetria
 - Associated conjugate nystagmus
 - Associated tremor
 - Sensory ataxia (peripheral neuropathy)
 - Spastic v waddling v ataxic gait
- Weakness
 - Flaccid v Spastic
 - Hemiplegia, Monoplegia, Diplegia
 - Proximal v distal
 - Mobility - wheelchair; assisted walking; independently mobile (age appropriate)
- Neuropathy
 - Mononeuropathy
 - Mononeuritis multiplex
- New epileptic seizures (since onset of disease)
 - Focal v Generalised
 - Focal - semiology; secondary generalisation
 - Generalised - GTCS, absence seizures
 - Frequency of seizure types
 - Response to medication

ECUSTEC Optometric and Ophthalmological Examination Worksheet

| | | | | | | |
|-----------------------|---|---|--|---|--|--|
| Hospital name: | | | | | | |
| Trial number: | <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> </tr> </table> | | | | | |
| | | | | | | |
| Date of Birth: | <table style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; border-bottom: 1px solid black;"> </td> <td style="width: 20px; border-bottom: 1px solid black;"> </td> <td style="width: 10px; border-bottom: 1px solid black; text-align: center;">/</td> <td style="width: 20px; border-bottom: 1px solid black;"> </td> <td style="width: 20px; border-bottom: 1px solid black;"> </td> </tr> </table> | | | / | | |
| | | / | | | | |

Please complete this worksheet for the day 60 assessment visit if the patient experienced CNS features during the acute disease (STEC HUS). Once completed, the paediatric neurologist responsible will use the information on the worksheet as Source Data from which to assign a CNS score for the ECUSTEC trial.

Visual acuity

| | | | |
|-----------|---------------------------------|-----------------------------------|---------------------------------------|
| Test used | | | |
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Eye alignment

| | | | |
|--------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Eye movement

| | | | |
|--------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Visual fields

| | | | |
|-----------|---------------------------------|-----------------------------------|---------------------------------------|
| Test used | | | |
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Anterior segment

| | | | |
|--------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Posterior segment

| | | | |
|--------|---------------------------------|-----------------------------------|---------------------------------------|
| Result | Normal <input type="checkbox"/> | Abnormal <input type="checkbox"/> | Not possible <input type="checkbox"/> |
| | | Details | |

Summary

| | | |
|--|-----------------------------|--|
| Does this child have a normal visual examination? | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> |
| If no, in your opinion (from parental reports and any available pre-morbid records) has this occurred since diagnosis of STEC HUS? | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> |

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ECUSTEC Neuropsychological Assessment Worksheet

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----------------------|---|--|--|--|--|--|--|--|--|--|--|--|--|---|--|--|--|--|--|--|--|--|--|--|--|
| Hospital name: | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trial number: | <table border="1" style="display: inline-table; margin: auto;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table> | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Date of Birth: | <table style="margin: auto;"> <tr> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> <td style="width: 20px; height: 20px; border-bottom: 1px dashed black;"></td> </tr> <tr> <td colspan="6" style="text-align: center;">/</td> <td colspan="6"></td> </tr> </table> | | | | | | | | | | | | | / | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| / | | | | | | | | | | | | | | | | | | | | | | | | | |

Please complete this worksheet for the day 60 assessment visit if the patient experienced CNS features during the acute disease (STEC HUS). Once completed, the paediatric neurologist responsible will use the information on the worksheet as Source Data from which to assign a CNS score for the ECUSTEC trial.

Age: _____ years _____ months

| | | |
|-----------|---|---|
| Form used | Parent/Primary Caregiver Ages 0-5 <input type="checkbox"/> | Parent form Ages 5-21 <input type="checkbox"/> |
|-----------|---|---|

| Scores | General Adaptive Composite | | |
|-------------|----------------------------|------------|---------------------|
| | Standard Score | Percentile | Confidence Interval |
| Pre-morbid? | | | |
| Current? | | | |

Summary

| | | |
|---|-----------------------------|--|
| Does this child have an ABAS-3 score below expected for age? | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> |
| If yes, in your opinion (from comparison with pre-morbid results) does this score since diagnosis of STEC HUS? | | |
| Yes <input type="checkbox"/> | No <input type="checkbox"/> | Unable to comment <input type="checkbox"/> |

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