TO BE PRINTED ON LOCAL TRUST HEADED PAPER

PATIENT (16-18YRS) INFORMATION SHEET

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

Invitation to take part in this research
We would like to invite you to take part in our research trial. Please take time to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part A

Summary of this research trial

Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (STEC HUS) is a sudden illness that develops in some people (often children and young people) after a gut infection caused by bacteria called STEC (Shiga-toxin producing E.Coli). People with STEC HUS often develop acute kidney injury – when the kidneys suddenly stop working properly – and some of these people need dialysis (artificial kidney treatment). Sometimes STEC HUS can cause complications in other parts of the body. Most people fully recover from STEC HUS but some will have long-term consequences and may need long-term specialist care.

Eculizumab is a medicine that blocks part of the immune (infection-fighting) system that seems to play a part in causing STEC HUS. Some doctors have given eculizumab to people with severe STEC HUS but not in a systematic way that can tell us whether it worked. We are testing eculizumab in a trial to see if it can make STEC HUS better.

The purpose of this trial is to see whether giving two doses of eculizumab to children and young people with STEC HUS reduces the severity of their disease. 134 children and young people with STEC HUS will be selected by kidney specialists at children's kidney units around the UK over a four year period. In addition to their normal care, they will receive either eculizumab or placebo (dummy treatment) within 48 hours of arriving at the children's kidney unit and a second dose of the same medicine a week later. In order to find out if eculizumab has been effective, information about each child's progress over the following 12 months will be collected by the team at the children's kidney unit and sent to the ECUSTEC trial co-ordination centre at the Birmingham Clinical Trials Unit (BCTU).

Thank you for reading so far – if you are still interested, please read the rest of this leaflet which gives more detailed information about the trial and what will happen if you decide to take part

Why have I been chosen?
You have been diagnosed with HUS and your doctors believe that this is likely to have been caused by STEC (proving STEC infection can take several weeks and your kidney specialist has made a diagnosis based on your symptoms).

Do I have to take part?
No, taking part in the research is entirely voluntary. It is up to you to decide whether to take part and your decision will not affect the standard to care you will receive. If you decide you should take part, you are free to withdraw you at any time and without giving a reason. If you do not take part or you withdraw from the trial, you will receive your consultant's usual treatment for STEC HUS and your decision will not affect your care in any way. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form.

What is the purpose of the trial?
STEC HUS can cause a number of serious health problems. The kidneys may suddenly fail or stop working properly needing dialysis (artificial kidney treatment). Other rare but serious complications in other parts of the body include diabetes (raised blood sugar, usually temporary), colitis (inflamed bowel, occasionally needing surgery), seizures (fits), problems with vision or a stroke. Most people fully recover from STEC HUS, but some will have long-term consequences and may need long-term specialist care. A figure showing the approximate frequency of these complications is shown below:

Figure 1: Frequency of dialysis, fits or other brain involvement and long term kidney damage in STEC HUS patients.

We are testing eculizumab to see if it can reduce the severity of STEC HUS, for example result in less time on dialysis or fewer participants developing complications in other parts of the body. Half the participants in the trial will receive two doses of eculizumab and half will receive two doses of placebo (dummy treatment) so that we can compare the outcome in both groups.

What is the drug or procedure that is being tested?
Eculizumab is a medicine that blocks part of the immune system called complement that seems to play a part in causing STEC HUS. It is a monoclonal antibody (a specially developed medicine that targets one substance) that is very effective in a related condition called atypical HUS. Some doctors have given eculizumab to people with severe STEC HUS but not in a systematic way that can tell us whether it worked.

What are the alternative treatments available?
People with STEC HUS benefit from supportive care (such as dialysis and treatment of other complications) from specialist health care teams but there is no treatment that is proven to prevent these complications from happening. Plasma exchange (PE) therapy is sometimes used for patients with severe STEC HUS however there are no published reports to say whether or not the use of PE is beneficial. If you take part in the trial you will not be given PE as it will remove the active drug and prevent the research from seeing if the drug works or not.

What are the possible benefits of taking part?
If eculizumab is found to be effective then your health may improve as a result of receiving a treatment which is not currently widely available. All patients in the trial will receive a greater level of vaccination against meningococcal infection than currently provided in the UK Immunisation Schedule. Although there is a short-term increase in the risk of meningococcal infection, participants will are likely to have a higher level of long-term protection against meningococcal infection than those who do not participate. People who take part in research trials such as this receive very regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals. Although you may not receive any individual benefit from taking part in the trial the information we get from the trial may help us to improve the treatment of all people with STEC HUS in the future.

What are the possible disadvantages and risks of taking part?
Participants may develop side-effects of eculizumab (see below) or of the vaccination and antibiotics given to prevent meningococcal infection. All participants will be monitored for side-effects and if there is any concern that these are in any way associated with the trial then you could be withdrawn from the trial.

What are the side effects of the treatment?
Eculizumab is generally well tolerated, although the following side effects have been reported: stomach upsets, cough, loss of appetite, runny nose, sore throat, headache, dizziness, tiredness, altered taste, pain in the joints or muscles, relatively few platelets in blood (thrombocytopenia), low white blood cell count (leukopenia), hair loss, itching, rash and flu-like symptoms. Allergic reactions are uncommon. People with STEC HUS may develop many of these symptoms anyway during the usual course of their illness.

Importantly, eculizumab treatment may temporarily reduce your natural resistance to infections, especially against "meningococcus", an organism that causes meningitis (infection of the linings of the brain) and septicaemia (blood infection). The risk of this infection is low – from information about patients treated with eculizumab for other conditions we estimate the risk of developing meningococcal infection is around one in 4,000 per patient in the trial.

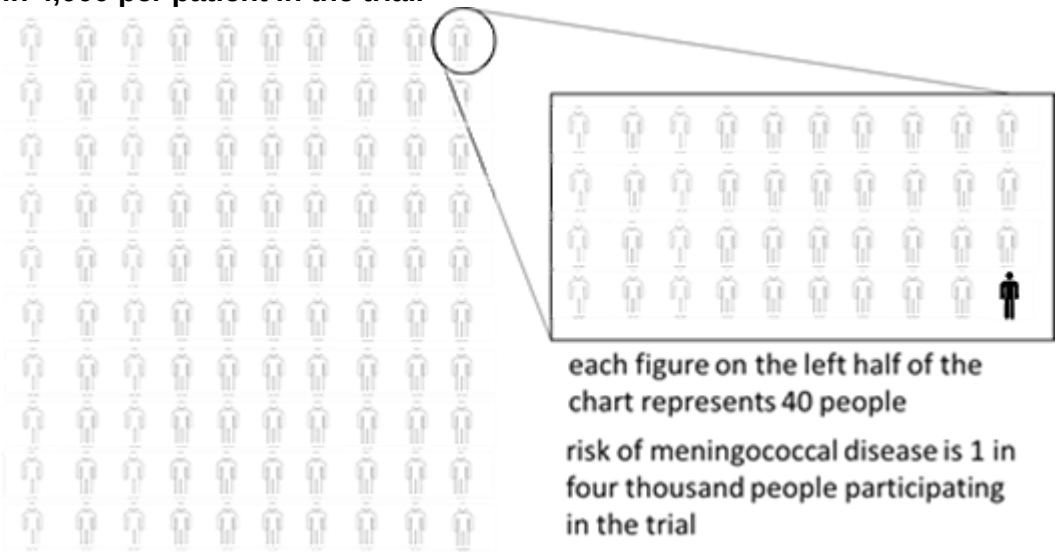

Figure 2: Estimated risk of developing meningococcal infection per patient receiving eculizumab in the trial.

The risk of meningococcal infection will return to the normal population risk 8 weeks after commencing the trial treatment. To ensure the risk of meningococcal infection is as low as possible going into the trial, you will be vaccinated against meningococcus.

The research team will liaise with your GP to determine which vaccines are necessary. To further reduce the risk of meningococcal infection, you will also receive 8 weeks of penicillin (taken twice daily by mouth, or an alternative if you are allergic to penicillin) and the first dose will be given before receiving the trial treatment (eculizumab or placebo). To make this trial the best possible test of which treatment is better, it is important to keep all treatments the same in both groups except eculizumab. Therefore people in both groups will receive vaccination and penicillin/alternative.

Side effects of meningococcal vaccination include sleepiness, headache, nausea, vomiting, diarrhoea, rash, pains in muscles and joints, irritability, injection site pain and redness. Side effects of penicillin include stomach upsets, stomach ache and allergy (rash, cough, wheeze, tightness in throat).

We will also give you information (on a card that you can carry with you) to recognise the signs and symptoms of meningococcal infection and advice about what to do in the unlikely event that you suspect you may have meningococcal infection. The card also contains clear information to guide health professionals in this situation. We will also notify your GP about this short term risk and the need to prescribe the preventative antibiotics.

What will happen to me if I take part?
If you agree to take part in the trial a computer will decide whether you receive active eculizumab or a placebo – a bit like tossing a coin. Neither you nor your doctor will know whether you have been given the eculizumab or the placebo, though this information can be found out if it is absolutely essential in an emergency. This is to make the trial the best possible test of which treatment is better.

The first injection will be given within 48 hours of you arriving at the children's kidney unit. This is because we think that the earlier eculizumab is given, the more effect it might have. You will receive a second injection of the same treatment (eculizumab or placebo) a week later. All participants, whether given eculizumab or placebo, will receive vaccination against meningococcus and will receive an 8 week course of twice daily low dose antibiotic by mouth to help prevent meningococcal infection (see "what are the side effects of the treatment" above).

All participants will be assessed regularly until discharge from hospital (the time until discharge varies depending on the course of the illness) and then at 1, 2, 6 and 12 months from enrolment to assess their progress. A summary of the follow-up visits for the ECUSTEC trial is given in Table 1 below.

As mentioned above, some patients who have STEC HUS can have fits or brain involvement. If you do experience any signs or symptoms of brain involvement (such as fits, problems with vision, a stroke) during your time in hospital, a full examination of the central nervous system (brain) including vision, hearing and psychological assessments, will be undertaken at the 2 month visit. Your parent/guardian will also be asked to complete a questionnaire about your behaviour.

The progress of STEC HUS is usually monitored with regular blood tests in hospital and during follow up. Participants in the trial will have daily *routine* blood tests whilst in hospital and at each follow up visit, in keeping with usual practice. Between day 1 and day 60 participants will have a 4-5ml, 1 teaspoon, sample of blood to analyse the genes associated with HUS. At 12 months a research blood sample will be taken to look at your kidney function.

At the 1 month assessment you will be asked to bring in a stool (poo) sample. You will be provided with a pot to collect the sample in and instructions on how to collect the sample. This sample will be sent to Public Health England Microbiological Reference Laboratory. We will ask you to complete two short questionnaires about your quality of life at six of the visits. This will take less than 20 minutes on each occasion.. At the 2 month visit, there will be an **optional** feedback questionnaire.

The rest of your treatment will be the usual treatment for STEC HUS.

Trial Follow-up Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**
	On the day that first dose is given	Daily whilst in hospital up to day 14*	Weekly whilst in hospital days 15 to 56**	Month 1	Month 2	Month 6	Month 12
Regular checkups that are part of the usual monitoring for STEC HUS	Y	Y	Y	Y	Y	Y	Y
Regular blood tests that are part of the usual monitoring for STEC HUS	Y	Y		Y	Y	Y	Y
Regular early morning urine tests that are part of the usual monitoring of STEC HUS (please bring a sample of your early morning urine to the clinic assessment)				Y	Y	Y	Y
Stool (poo) sample				Y			
Central nervous system examination by neurologist, assessment of vision, hearing and neuropsychology					Y***		
Research blood sample	Y	Y†		Y			
Research urine sample	Y	Y†		Y			
Two short questionnaires about your quality of life	Y	Y (day 7)		Y	Y	Y	Y
Short feedback questionnaire about your experience in the trial					Y		

Table 1: Y = Yes; * daily visits cease on discharge from hospital; ** only required if you remains an in-patient beyond day 14, cease upon discharge from hospital; *** only if you had central nervous system involvement during hospital stay; † Days 1,2,4,6,8 and 30.

For patients who are sexually active

Potential harm to the unborn child
For Girls

The effect of eculizumab on the development of an embryo, foetus or unborn child is currently unknown. Therefore, if you are a sexually active female of child-bearing potential, you must agree to not become pregnant for 6 months from enrolment into the trial. In addition, you must agree to use an effective and reliable method of birth control that has been agreed upon by the trial doctor for 6 months from enrolment into the trial. Some birth control methods that are acceptable for this trial are abstinence, the consistent use of an approved oral contraceptive (birth control pill or "the pill"), an intrauterine device (IUD), hormonal implants, contraceptive injection or a double barrier method (diaphragm with spermicidal gel or condom with contraceptive foam). The trial doctor will need to approve the method chosen. If you should become pregnant during the trial, the trial doctor should immediately be notified. No further doses of trial drug will be given and the progress of your pregnancy will be monitored until the outcome of the pregnancy is known**.**

Sexually active female patients must agree to undergo a pregnancy test within 48 hours prior to enrolment into the trial.

For Boys
If you are a sexually active male, you must inform your partner(s) (if she/they are female of child-bearing potential), that the effects of eculizumab on sperm are unknown. You or your partner(s) should use acceptable methods of birth control (as above), to avoid your partner(s) becoming pregnant for 6 months from enrolment into the trial.

Optional blood and urine samples
In addition to *routine* blood tests, an **optional** *research* blood sample and a sample of urine (if available) will be collected at several visits to look for further evidence of what causes STEC HUS. We will only collect these at a time when you are having blood tests for routine monitoring. **You can still take part in the study without giving a research blood or urine sample**. The amount of extra blood needed will be no more than 9ml (less than two teaspoonfuls).

Participants may be asked to give an additional, **optional**, one-off 10ml blood sample (two teaspoons) to undertake experiments to see how white blood cells from a patient affect kidney cells in the laboratory. The experiments on the samples would take place in Bristol.

Thank you for reading this far. We appreciate that trying to digest this information at such a difficult time for you is hard, but we want you to make the best informed decision. The additional information below will also need to be read at a suitable time for you, if you are still considering taking part in the trial.
Part B Supporting information

What if relevant new information becomes available?
Sometimes, during the course of a research project, new information becomes available about the treatment being studied. If this happens, your doctor will discuss how this affects your care and participation in the ECUSTEC trial. Your doctor might consider that you should continue in the trial or withdraw. Either way, he/she will explain the reasons and arrange for your care to continue. If you decide for you to continue in the trial he/she may ask you to sign an updated consent form. If the trial is stopped for any other reason, your doctor would, again, tell you and arrange your continuing care.

What will happen if I do not want to carry on with the trial?
You and you can decide not to continue with the trial at any time but, if you do, you can decide whether or not you would like your data collected so far to remain on file and be included in the final analysis.

Will my taking part in the trial be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential in the same way as your medical records. Information about your disease and progress will be sent by your doctors to the ECUSTEC trial office at the University of Birmingham Clinical Trials Unit, on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act. If you consent to you taking part in this trial, your GP and the other doctors involved in your clinical care will be notified of your participation and kept informed of your progress. With your permission, your relevant medical records may be inspected by authorised individuals from the Birmingham Clinical Trials Unit or your hospital. They may also be looked at by the trial team and regulatory authorities and representatives of the sponsor. The purpose of this is to check that the trial is being carried out correctly. All will have a duty of confidentiality to you as a research participant and will do their best to meet this duty.

The two short questionnaires completed by you at study visits will only be identified by your unique trial number and date of birth in the month/year format.

The local pharmacy team will securely send a certificate electronically confirming that vaccination has taken place and preventative antibiotics are being given to Alexion Pharmaceuticals (this is required by law). If a serious unexpected event occurs in a trial participant or if you (if female) become pregnant within 6 months of enrolment, the trial team may need to notify Alexion Pharmaceuticals. In all communication with the manufacturer you will only be identified by your unique trial number.

At the end of the trial, the data will need to be securely archived for 25 years. Arrangements for confidential destruction will then be made. Should you withdraw consent for your data to be used, none of your trial data, including that already collected, will be used for any trial purposes.

What if there is a problem?
If you wish to complain, or have any concerns about any aspect of the way you has been approached or treated during the course of this trial, the normal National Health Service complaints mechanisms is available to you. Taking part in this trial will not affect your legal rights. If you are harmed due to someone's negligence, then you may have grounds for a legal action.

If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions.

The contact details for the ECUSTEC Chief Investigator are: Dr Sally Johnson, Telephone 0191 282 4917.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

What happens when the trial stops?
When all the patients have completed the trial the results will be analysed and published in a scientific journal and used to help us to improve the treatment of participants and young people presenting with STEC HUS in the future. Your doctor can provide you with a copy of this publication if you are interested. We will also publicise the results on the trial's website. Only anonymous data will be published and your name will not appear in any report, presentation or publication.

If we discover that eculizumab does give a better outcome we will work with NHS commissioners to try to make this treatment available to participants who develop STEC HUS in the future. If it does not give a better outcome this will prevent people with STEC HUS being given an ineffective treatment and help focus research on other potential therapies. When the trial stops and the results have been published you can be told whether you received eculizumab or placebo if you are interested.

What will happen to the blood samples I give?
The optional blood samples will be processed and stored at your local centre and then sent to Bristol and the Newcastle Upon Tyne Hospitals NHS Foundation Trust for analysis. The optional urine sample will be processed and stored at your local centre and then sent to Bristol University for analysis. The blood sample at 12 months will be sent for analysis at East Kent Hospitals University NHS Foundation Trust. The additional 10ml optional blood sample which may be taken from some patients will be sent to the University of Bristol for analysis.

The blood sample collected between day 1 and day 60 will be sent to the University of Bristol (Professor Moin Saleem's laboratory) where the sample will be stored before being used to analyse the genes associated with HUS. If you agree, the DNA sample used to test genes

associated with HUS will undergo further **optional** detailed genetic tests, at an approved laboratory, of all potentially relevant genes to look for additional genes that might be involved in STEC HUS which may give clues to develop additional treatments in the future. Following completion of this work, any remaining DNA samples will be retained in the laboratory for use in future research projects investigating genetic factors and disease mechanisms in STEC HUS which may arise as a result of this work. This may include international collaborative studies. All such studies would require further Research Ethics Committee approval. Your samples will be identified only by your trial number and date of birth in the month/year format; samples will not be labelled with any personal information.

Who is organising and funding the research?
The ECUSTEC trial is being co-ordinated by the Birmingham Clinical Trials Unit at the University of Birmingham and is sponsored by the Newcastle Upon Tyne Hospitals NHS Foundation Trust. The Chief Investigator is Dr Sally Johnson at the Great North Children's Hospital. The trial is supported by the British Association for Paediatric Nephrology and the Children Specialty of the UK Clinical Research Network. The trial is being funded by National Institute for Health Research, Efficacy and Mechanism Evaluation Programme (NIHR EME). Funding for the eculizumab is provided by the NHS, not the manufacturer. The research has been reviewed and approved by all these organisations. Your doctor will not be paid for including you in this trial. The research is also supported by Haemolytic Uraemic Syndrome Help (HUSH) - The UK E-coli Support Group (http://www.ecoli-uk.com).

Who has reviewed the trial?
All research in the NHS is looked at by an independent group of people called a Research Committee to protect your safety, rights, wellbeing and dignity. This trial has been reviewed and given favourable opinion by North East – Newcastle and North Tyneside 1 Research Ethics Committee. Research Ethics Committees include healthcare professionals as well as non-medical people, and are completely independent from anyone organising the trial.

Where can I get further information?
General information about STEC HUS can be found at www.infokid.org.uk/STEC-HUS and at www.ecoli-uk.com.

For queries about the trial or for further information please contact:

Dr Sally Johnson, Telephone 0191 282 4917, ECUSTEC Chief Investigator

<Insert Local PI Name>, Telephone <Insert Local PI Tel. No.>, ECUSTEC Principal Local Investigator

The ECUSTEC trial co-ordinating centre is located at the Birmingham Clinical Trials Unit, College of Medical & Dental Sciences, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham B15 2TT. Tel 0121 415 9132, Fax: 0121 415 9135, Web address: www.birmingham.ac.uk/ECUSTEC.

Thank you for considering participation in this trial

You will be given a copy of this information sheet and a signed consent form to keep if you decide to take part in the trial.