NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

Specification for manufacturer/sponsor submission of evidence

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Instructions for manufacturers and sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the manufacturer or sponsor to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme' available at: (http://www.nice.org.uk/media/188/49/HST_combined_Interim_Process_and_Methods_FINAL_31_May_2013.pdf). After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with 'see appendix X'. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').
The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.
If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in

confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document 'Related procedures for evidence submission'.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Glossary of terms

Term	Definition
ADAMTS13	A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs [13th member of the family]
AE	Adverse Event
AGNSS	Advisory Group for National Specialised Services
aHUS	atypical Haemolytic Uraemic Syndrome
aHUSUK	UK aHUS Patients and Families Support Group
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AWMSG	All Wales Medicines Strategy Group
BIM	Budget Impact Model
CASP	Critical Appraisal Skills Programme
CDC	Centers for Disease Control
CFH	Complement Factor H
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CPAG	Clinical Priorities Advisory Group
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
CVD	Cardiovascular Disease
DGKε	Epsilon isoform of diacylglycerol kinase
eGFR	estimated Glomerular Filtration Rate
EHA	European Haematology Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life Group 5 Dimensions Self-Report Questionnaire
ESRF	End-Stage Renal Failure
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence-Activated Cell Sorting
FDA	United States Food and Drug Association
GI	Gastrointestinal
GLS	Generalised Least Squares
GRADE	Grading Recommendations Assessment, Development, and Evaluation
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelets
HIV	Human Immunodeficiency Virus
HRG	Healthcare Resource Groups
HRQL	Health-Related Quality of Life
HS	Health State
HSTP	Highly Specialised Technology Policy
HU	Health Utility
HUS	Haemolytic Uraemic Syndrome

Term	Definition
ICER	Incremental Cost-Effectiveness Ratio
IFR	Individual Funding Request
IQR	Interquartile Range
ITT	Intent-To-Treat
IVIG	Intravenous Immunoglobulin
LB	Lower Bound of confidence interval
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LOWESS	Locally Weighted Scatterplot Smoothing
LY	Life Years
LYG	Life Years Gained
MAVE	Major Adverse Vascular Events
MID	Minimally Improved Difference
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NR	Not Reported
OLS	Ordinary Least-Squares
PbR	Payment By Results
PCR	Polymerase Chain Reaction
PCT	Primary Care Trust
PD	Pharmacodynamics
PE	Plasma Exchange
PI	Plasma Infusion
PLEX	Plasma Exchange
PK	Pharmacokinetics
PNH	Paroxysmal Nocturnal Haemoglobinuria
PP	Per-Protocol
PRISMA	Preferred Reporting Items of Systematic reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QoL	Quality of Llife
RaDaR	UK Registry for Rare Kidney Diseases
RCT	Randomised Controlled Trial
RRT	Renal Replacement Therapy
SD	Standard Deviation
SE	Standard Error

Term	Definition
SF-36	Short Form-36 Questionnaire
SLE	Systemic Lupus Erythematosus
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	Standard of Care
STEC	Shiga-Toxin producing enterohaemorrhagic *Escherichia coli*
STEC-HUS	Shiga-Toxin producing enterohaemorrhagic *Escherichia coli*-induced HUS
TEAE	Treatment-Emergent Adverse Events
TMA	Thrombotic Microangiopathy
TTO	Time Trade Off
TTP	Thrombotic Thrombocytopenic Purpura
UB	Upper Bound
UK	United Kingdom
ULN	Upper Limit of Normal
USRDS	United States Renal Data System

Executive Summary

Please include a brief summary of the key points in the submission addressing:

- *Nature of the condition*
- *Impact of the new technology*
- *Cost to the NHS and Personal Social Services*
- *Value for money*
- *Impact of the technology beyond direct health benefits*
- *Impact of the technology on the delivery of specialised services*

All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) was launched in the United Kingdom (UK) at the time of the marketing authorization approval in November 2011. The Advisory Group for National Specialized Services (AGNSS) recommended to Health Ministers in June 2012 that eculizumab be nationally commissioned for all patients with aHUS, taking into account the severity of aHUS and the significant clinical benefits provided by this lifesaving therapy. Similarly, the Clinical Priorities Advisory Group (CPAG) recommended in July 2013 that eculizumab be routinely funded for: (1) new patients with atypical haemolytic uraemic syndrome (defined to include those with a functioning kidney); and (2) existing patients who are on dialysis and are suitable for a kidney transplant. This recommendation was ratified by National Health Service (NHS) England and the policy entitled "Clinical Commissioning Policy Statement Eculizumab for atypical haemolytic uraemic syndrome" was published on 11th September 2013. As such, Alexion respectfully requests that the National Institute for Health and Care Excellence (NICE) follow the recommendations made by both the AGNSS and the CPAG, and commission the use of eculizumab in aHUS for patients in England desperately in need of treatment to avoid the well-documented, poor prognosis associated with aHUS.

Alexion is well aware that the factors affecting reimbursement for the very limited number of therapies available for ultra-rare diseases are complex. As a result, we have partnered closely and effectively with multiple countries worldwide to recognise the life-saving and life-improving value of eculizumab for their citizens, resulting in effective and broad access to the treatment that is also consistent with varied affordability and cost containment objectives. These countries have considered such issues as: (1) the devastating and life-threatening nature of aHUS; (2) the overwhelming clinical and life-saving benefits of eculizumab; (3) the very small number of patients with aHUS; (4) the clear lack of available and effective treatment alternatives; and, (5) the ethical imperative to provide hope to the sickest citizens and to ensure that this hope does not discriminate between patients with the rarest diseases and patients with more common diseases. Alexion seeks the same partnership and dialogue with the NHS, and is confident that after examining the clinical benefits associated with eculizumab treatment, NICE will also recommend to the NHS that aHUS patients be given access to eculizumab.

Product Characteristics (Sections: 2.3, 12.3.4, and Summary of Product Characteristics *(SmPC))*

Eculizumab (Soliris®) received European Medicines Agency (EMA) approval on November 24, 2011 for the treatment of atypical haemolytic uraemic syndrome (aHUS). An overview of details about eculizumab, as outlined in the SmPC, for aHUS is provided in the Table 1:

Table 1: Summary of Eculizumab for aHUS Product Characteristics

Pharmaceutical Formulation	30 mg/mL concentrate (300 mg per 10 mL vial); Clear, colourless, pH 7.0
Mechanism of Action	Terminal complement inhibitor that specifically binds to the terminal complement protein C5 with high affinity, thereby inhibiting its cleavage to pro inflammatory and pro thrombotic C5a and C5b molecules and preventing the generation of the lytic as well as pro-inflammatory and pro-thrombotic terminal complement complex C5b-9.
Method of Administration	Intravenous (IV) infusion at final concentration of 5 mg/mL
Doses	The aHUS dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase: • Initial phase: 900 mg of Soliris administered via a 25 – 45 minute IV infusion every week for the first 4 weeks. • Maintenance phase: 1,200 mg of Soliris administered via a 25 – 45 minute intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute IV infusion every 14 ± 2 days • Paediatric Paroxysmal Nocturnal Haemoglobinuria (PNH) and aHUS patients with body weight ≥ 40kg are treated with the adult dosing recommendations, respectively. • In paediatric PNH and aHUS patients with body weight below 40 kg, dose is adjusted according to body weight
Dosing Frequency	• Initial phase: every week for the first 4 weeks. • Maintenance phase: infusion for the fifth week, followed by infusion every 14 days ± 2 days
Repeat Courses of Treatment	Eculizumab for aHUS is recommended by the EMA to continue for the patient's lifetime
Product Restrictions	Eculizumab is contraindicated in aHUS patients: • With unresolved *Neisseria meningitidis* infection; and • Who are not currently vaccinated against *Neisseria meningitidis* or do not receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.
Acquisition Cost	One 300 mg vial of eculizumab is currently priced at £3,150 (excluding value added tax (VAT)).

Nature of the Condition

About Complement System (Section 6.1)

Patients with aHUS have chronic uncontrolled complement activation causing on-going platelet, endothelial and white blood cell activation, leading to inflammation and thromboses (blood clots) in small blood vessels throughout the body, a process known as systemic thrombotic microangiopathy (TMA).(Noris and Remuzzi, 2009; Karpman et al, 2006; Stahl et al, 2008; Stahl et al, 2011) As a result of ongoing complement-mediated TMA, aHUS patients are at constant risk of sudden and

progressive damage and failure of multiple vital organs.(Noris et al, 2010; Sellier-Leclerc et al, 2007; Neuhaus et al, 1997; Noris and Remuzzi, 2009)

aHUS Morbidity and Disability with Current Standard of Care (Section 6.1)

Historical management of aHUS has been limited to supportive care only, including plasma exchange/plasma infusion (PE/PI), chronic dialysis, or kidney transplantation, none of which target chronic uncontrolled complement activation nor positively impact the morbidities or mortality of aHUS. These supportive care options are clinically inadequate, life-disrupting, and pose significant safety risks.(Michon et al, 2007; George et al, 2008; Noris and Remuzzi, 2009) aHUS affects both children and adults and has a very poor prognosis, demonstrated by the fact that 33% to 40% of aHUS patients die or progress to end stage renal failure (ESRF) requiring dialysis with the first aHUS clinical manifestation.(Caprioli et al, 2006; Noris et al, 2010) The chronic nature of aHUS results in progressive, on-going morbidity as 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on PE/PI or dialysis and a progressive increased mortality rate thereafter.

Quality of Life for aHUS Patients and Caretakers (Section 7.1)

aHUS is associated with significant impairment of quality of life for patients through the frequent and severe morbidities, including renal impairment and the impact of aHUS on other vital organs. The lives of aHUS patients also are impacted significantly by ineffective supportive care measures, specifically PE/PI and dialysis. As described in Section 7, feedback from interviews with aHUS patients in the UK highlights the frequency and nature of side effects of PE/PI sessions, and the burden of dialysis as drivers for their poor quality of life. Specifically, patients are usually unable to perform normal daily activities after treatment. In addition to the physical debilitations from PE, some patients experience psychological trauma for fear of relapsing and reinitiating treatment.

Both PE/PI and dialysis result in a substantial burden being placed on informal carers and families of aHUS patients. In a survey of UK aHUS caretakers, informal carers (spouse or relative) reported spending on average 68 hours per week supporting their aHUS relative. As a result, a majority of these carers reported they had to reduce their work activities in order to provide the necessary care often causing physical, emotional and financial hardship on their entire family.

Extent and Nature of Current Treatment Options (Section 8.1)

Clinical guidelines released in 2009 by the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society included recommendations for the investigation and management of aHUS patients in the UK prior to the availability of eculizumab for aHUS.(Taylor et al. 2009) The recommendations highlight that PE/PI is only considered an empirical treatment for aHUS with limited therapeutic value, receiving a weak recommendation. Transplant avoidance was given a strong recommendation as the risk of allograft loss post-transplantation is high in all aHUS patients, regardless of identified complement mutation.(Taylor et al. 2009) The ineffectiveness of current treatment options is demonstrated by the documented on-going morbidity and mortality, whereby 33% to 40% of aHUS patients die or progress to ESRF requiring dialysis with the first aHUS clinical manifestation, despite the use of PE/PI in the vast majority of these patients.(Caprioli et al, 2006; Noris et al, 2010)

Impact of the New Technology

Clinical Effectiveness of Eculizumab (Sections 9.6 and 9.9)

Eculizumab is designed to block activation of the terminal stage of the complement system directly and potently.(Rother et al, 2007) As a result, use of eculizumab reduces the underlying systemic complement-mediated TMA process and subsequently can reverse or prevent further kidney damage, which has been shown to lead to a discontinuation or avoidance of dialysis. Eculizumab has also been shown to prevent progression of other organ damage in aHUS patients, and has demonstrated a reduction or elimination in the need for PE/PI as well as a significant improvement in patients' quality of life.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011; Alexion, 2012; Legendre et al, 2013)

Overall Magnitude of Health Benefits to Patients and Carers (Section 7.2)

In the two prospective controlled clinical trials assessed for product registration (C08-002 and C08-003), eculizumab demonstrated the ability to:

- Inhibit complement activation in all treated aHUS patients;
- Inhibit complement-mediated TMA;
- Significantly improve renal function (including discontinuation of dialysis);
- Prevent disease progression (including avoidance of dialysis);
- Significantly reduce or eliminate requirements for burdensome PE/PI;
- Improve systemic organ function (including neurologic and gastrointestinal complications);
- Significantly improve health-related quality of life; and
- Demonstrate long-term safety and tolerability.

For carers, eculizumab reduces the emotional stress and burden (both physical and financial) of caring for an aHUS family member, bringing normality back to everyday life.

Health Benefits across aHUS Populations (Sections 9.6 and 9.9)

Medical evidence demonstrates that eculizumab has significant clinical benefits regardless of aHUS disease history, previous renal transplant or genetic background. The eculizumab prospective and retrospective registration trials (C08-002, C08-003, and C09-001r) were comprised of a diverse patient population expected to be seen in the medical practice setting including:

- Patients with short disease duration, haematologic evidence of TMA, and progressive renal impairment;
- Patients with long duration of aHUS, chronic renal impairment, and long-term PE/PI;
- Patients with and without history of renal transplant; and,
- Patients with and without identifiable genetic mutation.

Clinical efficacy was demonstrated across all patient populations. No significant differences in efficacy were identified by presence or absence of complement system abnormality (i.e., identified genetic mutation) or in patients with native or transplanted kidneys.(Goodship et al, 2012; Legendre et al, 2013)

It is recognized that approximately 50% to 70% of patients with aHUS do not have an identifiable mutation.(Noris and Remuzzi, 2009; Noris et al, 2010; Fremeaux-Bacchi et al, 2013) Therefore, lack of an identifiable mutation is not in itself a cause to rule out the diagnosis of aHUS or use of eculizumab. Genetic testing is also time consuming, taking weeks to months to perform, making it inappropriate to inform treatment decisions in a disease that can, and does, rapidly advance to ESRF, other organ damage, and mortality following diagnosis.

Robustness of the Current Evidence and the Contribution the Guidance Will Have (Sections 8.4 and 9.9.3)

The clinical trials of eculizumab are the only prospective clinical trials performed in aHUS and the first and only studies to demonstrate a well-tolerated and efficacious treatment designed to specifically inhibit complement-mediated TMA in aHUS patients. The clinical trial programme included a broad range of aHUS patients in both prospective and retrospective medical practice settings. Owing to the rarity, severe and life-threatening nature of the disease, as well as the already available evidence of efficacy and positive outcomes with eculizumab treatment reported in several published case studies, it was not ethically possible to perform a randomised placebo controlled trial, excluding critically ill patients from receiving therapy.

Eculizumab therapy resulted in significant inhibition of TMA, improved or stabilised renal function, elimination of or avoidance of progression to dialysis, and improved patient quality of life in patients immediately after presentation of TMA, as well as those with a longer duration of disease from time of diagnosis. These benefits were similar in patients with milder renal impairment compared to those with severe renal impairment; and patients with native kidneys compared with one or multiple prior transplants.(Legendre et al, 2013) Interim analyses from more recent unpublished prospective studies demonstrate similar clinical benefit in paediatric and adult aHUS populations including patients treated without prior use of PE/PI (prospective studies C10-003 and C10-004, respectively). Investigators in the clinical trials report that earlier intervention with eculizumab results in greater improvement in renal function but clearly note that all patients benefit.(Legendre et al, 2013) Therefore, clear evidence from prospective trials, numerous published case studies, and data from the medical practice setting, demonstrate that eculizumab is now the SOC in the treatment of aHUS. Eculizumab is considered first-line treatment, and one which should be rapidly used in all patients diagnosed with aHUS.

Treatment Continuation Rules (Section 10.1.16)

Eculizumab is recommended and approved as chronic lifetime therapy.(SmPC, 2013) Medical evidence demonstrates that despite the use of supportive care there is a progression of the deleterious effects of aHUS with continued on-going risk of TMA and subsequent life threatening complications.(Noris and Remuzzi, 2009; Noris et al, 2010; Hovinga et al, 2010; Legendre et al, 2013; SmPC, 2013) Prospective trial data demonstrate that chronic treatment with eculizumab can improve and continue to improve renal function and patient quality of life even after two years of chronic treatment. In contrast, reports of recurrence of TMA and on-going evidence of complement-mediated TMA following discontinuation of eculizumab treatment have been observed, strengthening the evidence for the need to continue chronic eculizumab treatment.

Costs to the National Health Service and Personal Social Services (PSS)

Budget Impact in the NHS and PSS (Section 13.7)

Due to the ultra-rare nature of aHUS, and therefore the limited number of patients who will benefit from this life-saving therapy, eculizumab is expected to have an overall limited five-year budget impact in England as follows:

[redacted]

Robustness of Costing and Budget Impact Information (Section 13.8)

The availability of eculizumab for aHUS has been shown to significantly reduce the morbidities suffered by patients with aHUS, as seen in the cost-effectiveness model in Section 12; however, the cost-effectiveness model excluded indirect costs, which would likely be greatly reduced as a result of eculizumab therapy. Also, health utility and non-direct medical costs (i.e., indirect costs) are excluded from the budget impact model (BIM), which therefore then fails to illustrate adequately the extensive value of treatment for these patients both individually and in terms of societal impact. Moreover, due to the abbreviated time horizon of the BIM, the total life-years lost by standard of care (SOC) are not included from a budget perspective. Indirect costs also would likely be reduced by eculizumab given its substantial improvement in patients' quality of life; however, there are no published studies which quantify these effects in a form that could be included in the BIM. Consequently, these collective effects are not included in the current analysis, and the budget impact of the eculizumab scenario is likely to underestimate the impact of eculizumab therapy as a result.

Value for Money

Two analyses were conducted to assess the "Value for Money" of eculizumab in the treatment of aHUS: (1) incremental clinical benefit of eculizumab vs. SOC; and; (2) cost comparison of eculizumab vs. SOC. Modelling and extrapolation beyond the eculizumab clinical data were required to complete these two analyses. Importantly, "value for money" must be appropriately weighted to support positive clinical outcomes, not just lower overall expenditures.

Technical Efficiency (Section 12.5.7 and 12.8.1)

The incremental benefits of eculizumab compared to current treatment (SOC) are (discounted) 25.22 quality-adjusted life years (QALYs). In summary, the model predicts very large benefit increases for eculizumab patients, in QALYs, life-years and reduced time in the ESRF health state. These predicted benefit gains were robust in univariate, multi-way, and probabilistic sensitivity analysis. The relative size of the gains is very large compared to other healthcare innovations, as demonstrated through data at the Tufts University's Cost-effectiveness Registry. The source of the gains is an increase in quality-of-life as observed in the eculizumab trials (Legendre et al, 2013), and a predicted increase in lifespan.

Productive Efficiency (Section 12)

The nature and extent of the other resources needed to enable eculizumab to be used is very limited within the current structure of the NHS. Eculizumab is simple to administer, can be delivered via a homecare provider (funded by Alexion via the aHUS homecare initiative), and should be administered under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders if administered in the hospital setting. Early and accurate diagnosis and treatment of aHUS is an important element which could be supported by centre/s of expertise within England, as is currently the case with the adult and paediatric centres based in Newcastle and led by Professor Tim Goodship, MD and Dr. Sally Johnson, respectively.

Allocative Efficiency (Section 12.5.7)

The impact of eculizumab on the budget available for specialised commissioning ranges from [redacted] in the first model year to [redacted] in the fifth model year. These amounts are consistent with budget allocated for the treatment of other commissioned services to treat very rare conditions, for example lysosomal storage disorders. Additionally, eculizumab for the treatment of aHUS represents good value for money as a result of demonstrated efficacy in several key factors, including:

- The high response rate in treated patients;
- The compelling clinical benefit which may completely alter the disease course of aHUS;
- The ability to positively impact on the quantity and quality of life of aHUS patients, and;
- The high tolerability of eculizumab therapy and minimal impediment to patient or family/carer quality of life, particularly when compared to prior supportive care options.

[redacted]. The economic model submitted estimates that conditional on being alive, eculizumab reduces non-biologic direct medical costs by 80%. These costs are based on eculizumab-treated patients spending less time in more costly health states like ESRF, transplant, and chronic kidney disease (CKD) stages 3a-4, and more time in CKD stages 0-2.

Impact of Eculizumab Beyond Direct Health Benefits

Significant Benefits beyond Health Outcomes (Section 7.1)

The emotional and physical stress currently experienced by aHUS patients and their carers would be largely mitigated if not resolved should the NHS commission eculizumab for the treatment of aHUS. In the aHUS patient and carer survey conducted, many family members of patients with aHUS reported particularly distressing experiences of caring for—and in some cases losing— children and other family members with aHUS, and also how multiple members of their family had been negatively affected by the disease over several generations. Additionally, as aHUS is such a debilitating disease, patients are unable to work while suffering severe TMA manifestations of aHUS. As a result many family members have had to give up their own work to care for them, crippling their family's' finances.

Proportion of Costs Incurred Outside of the NHS and PSS (Sections 14.1 - 14.4)

The impact of aHUS has been quantified by estimating societal costs and out-of-pocket expenditures for patients and carers, and estimate cost savings that might be possible with eculizumab. For example, Alexion estimates total annual savings for government (non-NHS) and societal costs associated with aHUS by eculizumab as follows:

- Patient lost productivity: £784,400
- Current carer lost productivity: £1,597,729
- Ex-carer lost productivity: £804,010
- Patient receipt of government benefits: £904,280
- Carer receipt of government benefits: £248,411
- Lost tax revenues for patients: £279,246
- Lost tax revenues for carers: £284,396

Alexion also quantifies the savings that might be possible as a result of eculizumab therapy with respect to: (1) societal costs including, productivity loss, foregone tax revenue, and government benefits; (2) out-of-pocket expenditures for patients and carers including, transportation, housing and other costs; and, (3) other carer costs including informal care, average health care service use, and social opportunity cost.

Long-term Benefits to NHS of Research and Innovation (Sections 14.6-14.7)

In terms of innovation to the NHS specifically, the aetiology of aHUS was unknown 15 years ago. In 1998, the Newcastle group led by Professor Tim Goodship was the first to identify a mutation in the gene encoding the complement regulator factor H.(Warwicker et al, 1998) Since then, a series of studies have established that approximately 50% to 70% of aHUS patients have either an inherited or acquired abnormality of complement that is associated with over-activity of the complement system.(Noris and Remuzzi, 2009; Noris et al, 2010; Fremeaux-Bacchi et al, 2013) These findings provided the logic for the recent clinical trials of eculizumab to inhibit complement-mediated TMA in aHUS.

Establishing the routine use of eculizumab for the management of aHUS within England will maintain and enhance the international reputation that the UK has in the field of aHUS. The proposed commissioning of eculizumab and potential development of a service based on centre/s of expertise for aHUS will have an impact on the development of disease-specific working groups, care pathways, and the UK Registry for Rare Kidney Diseases (RaDaR). With NHS Kidney Care, care pathways are also being developed for aHUS which will become an integral part of the service. Alexion is also sponsoring an international aHUS registry that will capture and continue to follow aHUS patients irrespective of treatment status. The objectives of the aHUS registry are three-fold: (1) to better characterize the natural history of aHUS in patients not treated with eculizumab, (2) to better characterize how eculizumab will impact aHUS disease progression and the safety of eculizumab, and (3) to better characterize how eculizumab will contribute to the current understanding of the role of complement-mediated TMA in aHUS disease progression.

Impact of Eculizumab on the Delivery of a Specialised Service

Staffing and Infrastructure Requirements, Including Training and Planning for Expertise (Sections 15.1-15.2)

Eculizumab is simple to administer via intravenous (IV) infusion and is generally well-tolerated. It is therefore suitable for administration at appropriate centres throughout England and should be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders. In addition, world-renowned aHUS experts in the UK currently offer support and advice to renal and haematology colleagues across England as part of an informal referral service for the diagnosis and management of aHUS including a national prescription management service for eculizumab.

Infrastructure requirements are limited to the additional resource requirements within centre/s of expertise which might be designated by NHS England to run a national aHUS service, whereby such centres would need full-time equivalent (FTE) resources to ensure adequate and immediate support of local centres on a constant basis (24 hours a day, 7 days a week).

No additional staffing and infrastructure requirements will be needed in local centres where aHUS patients may present.

Conclusion

The significant morbidities and mortality associated with aHUS, despite best available supportive care, represents an unmet medical need for patients with this ultra-rare and life-threatening disorder. As the only EMA-approved and proven treatment for aHUS, eculizumab fulfills this critical clinical need and dramatically improves the quality of life for patients and their families devastated by this disease. Therefore, Alexion urges NICE to recommend national commissioning for use of eculizumab in aHUS for patients in England in need of treatment with this novel biologic therapy to avoid the well-documented very poor prognosis associated with the disease.

Section A – Decision problem

Section A describes the decision problem, the technology, on-going studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Children and adults with atypical haemolytic uraemic syndrome (aHUS)	No variation from final scoping document.	N/A
Intervention	Eculizumab (Soliris®)	No variation from final scoping document.	N/A
Comparator(s)	Newly diagnosed people who have not received prior treatment: • plasma infusion and/or exchange Previously treated people with kidney impairment: • kidney dialysis • kidney or kidney/liver transplantation	No variation in the content has occurred from the final scoping document, only in the way the information is presented; the available data in aHUS related to plasma infusions/exchange, dialysis, kidney transplantation and kidney/liver transplantation are all contained within the submission (mostly under Section 6.1).	Current data available, and actual clinical practice, do not allow this information to be presented in the distinct groups/format described in the final scoping document, especially with regards to newly diagnosed patients who have not received prior treatment.
Outcomes	The outcome measures to be considered include: • overall survival • time to disease recurrence • response to treatment • avoidance of dialysis • avoidance of plasma therapy • maintenance or improvement of kidney function • other major non-renal clinical outcomes • eligible for/success of transplantation • development of antibodies and resistance	Data are not available for some of the outcomes measures outlined in the scoping document including time to disease recurrence, and eligible for/success of transplantation. These outcomes measures are discussed in context of the data available and addressed specifically in section 9.9.3.	Current data available, and actual clinical practice, do not allow this information to be presented in the distinct groups described in the final scoping document, especially with regards to disease recurrence, avoidance of PE/PI when eculizumab is used as first-line treatment, and non-renal clinical outcomes as they are not available in the limited data for standard of care or were not included as the primary or secondary endpoints in the eculizumab clinical trials.
Subgroups to be considered	N/A	N/A	N/A
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carers' quality of life • extent and nature of current treatment options	No variation from final scoping document.	N/A
Cost to the NHS and PSS, and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if	No variation from final scoping document.	N/A

	applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.	No variation from final scoping document.	N/A
Special considerations, including issues related to equality	N/A	N/A	N/A

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Soliris® (eculizumab)

Therapeutic class: Complement inhibitor

Anatomical Therapeutic Chemical (ATC) Classification:

L04AA25

L	Antineoplastic and immunomodulating agent
L04	Immunosupressants
L04A	Immunosupressants
L04AA	Selective immunosuppressants
L04AA25	Eculizumab

2.2 What is the principal mechanism of action of the technology?

Eculizumab is a first-in-class human monoclonal antibody that selectively and potently arrests terminal complement activation. In aHUS, impairment of the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in chronic platelet activation, endothelial cell damage and thrombotic microangiopathy (TMA). In aHUS patients, uncontrolled terminal complement activation and the resulting complement mediated TMA are blocked with eculizumab treatment.

Eculizumab is a terminal complement inhibitor that specifically binds to the terminal complement protein C5 with high affinity, thereby inhibiting its cleavage to pro inflammatory and pro thrombotic C5a and C5b molecules and preventing the generation of the lytic terminal complement complex C5b-9. By targeting the terminal C5 protein, eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

On September 23, 2011, the United States Food and Drug Association (FDA) approved eculizumab for the treatment of children and adults with aHUS to inhibit complement-mediated TMA. Approval by the European Medicines Agency (EMA) was obtained shortly thereafter on November 24, 2011, stating “Soliris (eculizumab) is indicated for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS)”.(SmPC, 2013) In recognition of the chronic nature of aHUS and the on-going substantial risk of mortality and significant morbidities, the Soliris Summary of Product Characteristics (SmPC) states that eculizumab treatment is recommended to continue for the patient’s lifetime.

2.3 Please complete the table below.

Table A2: Dosing information of technology being evaluated

Pharmaceutical formulation	30 mg/mL concentrate (300 mg per 10 mL vial); Clear, colourless, pH 7.0
Method of administration	IV infusion at final concentration of 5 mg/mL

Doses	The aHUS dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase: • Initial phase: 900 mg of Soliris administered via a 25 – 45 minute intravenous infusion every week for the first 4 weeks. • Maintenance phase: 1,200 mg of Soliris administered via a 25 – 45 minute intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute intravenous infusion every 14 ± 2 days (see section 5.1) Paediatric PNH and aHUS patients with body weight ≥ 40kg are treated with the adult dosing recommendations, respectively. In paediatric PNH and aHUS patients with body weight below 40 kg, dose is adjusted according to body weight (See dosing table below)
Dosing frequency	• Initial phase: every week for the first 4 weeks. • Maintenance phase: infusion for the fifth week, followed by infusion every 14 ± 2
Average length of a course of treatment	Eculizumab for aHUS is recommended by the EMA to continue for the patient's lifetime
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	See dosing table below for paediatric weight-based dose. Supplemental dosing is required

Table A3: EMA-approved dosing recommendations for aHUS

Body Weight	Induction Dosing	Maintenance Dosing
For Patients Less Than 18 Years of Age		
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks
For Patients 18 Years of Age and Older		

Body Weight	Induction Dosing	Maintenance Dosing
All body weights	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Approval from the EMA for use of eculizumab in aHUS was granted on November 24, 2011.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Not applicable as eculizumab for aHUS is already in use in the UK.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes. In addition to approval by the EMA on November 24, 2011, regulatory approval has been granted for use of eculizumab for aHUS in the countries listed below. The date of regulatory approval in each country is also listed.

- United States (September 23, 2011)
- Israel (December 29, 2011)
- Switzerland (May 25, 2012)
- Australia (November 22, 2012)
- Canada (March 1, 2013)
- Colombia (June 17, 2013)

3.4 If the technology has been launched in the UK provide information on the use in England.

Eculizumab for the treatment of aHUS was launched in the UK at the time of the marketing authorization approval in November 2011. The Advisory Group for National Specialised Services (AGNSS) received a full submission in January 2012 and completed a full evaluation of eculizumab for the treatment of aHUS which was announced in January 2013. The AGNSS evaluation concluded that eculizumab should be routinely commissioned by the NHS; however, a Ministerial decision was made to pass eculizumab to NICE for additional evaluation at the same time. Since the launch of eculizumab for aHUS in November 2011, eculizumab use has been restricted to individual patient funding via the primary care trust (PCT) individual funding request (IFR) process up until April 2013. In April 2013, NHS England became the responsible authority under the terms of the new Health and Social Care Act to review IFRs for use of eculizumab in aHUS patients in England.

NHS England reviewed its position regarding the funding of eculizumab over a period of three months before the Clinical Priorities Advisory Group (CPAG) provided a

recommendation, similar to that already proposed by AGNSS, to the Directly Commissioned Services Group that eculizumab should be routinely funded for:

- New patients with atypical haemolytic uraemic syndrome (defined to include those with a functioning kidney); and
- Existing patients who are on dialysis and are suitable for a kidney transplant.

A commissioning for evaluation scheme will be developed for patients who are not suitable for transplant.

The policy of NHS England entitled "Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome" was published on 11th September 2013.

Given that the policy is extremely recent, the impact on uptake of eculizumab within NHS England has yet to be fully seen.

The Budget Impact Model provided with this submission provides projected data on anticipated uptake within England and contains a projection for year end 2013 whereby 44 aHUS patients will have received treatment with eculizumab since November 2011.

4 Ongoing studies

4.1 Provide details of all completed and on-going studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Overview of Eculizumab aHUS Clinical Studies

Alexion conducted two controlled, prospective, open-label, Phase II, multi-centre clinical trials (C08-003A/B and C08-002A/B) to demonstrate the safety and efficacy of eculizumab in 37 patients with aHUS.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011; Alexion, 2012; Legendre et al, 2013) These studies were the only controlled and prospective studies to be undertaken for any treatment approach in aHUS. These trials were designed collaboratively with aHUS experts in the field and were based on the extremely rare prevalence of aHUS, the challenge of recruiting patients with this ultra-rare disease, and the prior publication of several case reports strongly indicating a therapeutic benefit of eculizumab in a small number of aHUS patients. Both trials were conducted in adult and adolescent (≥12 years old) patients who had a diagnosis of aHUS, with or without identifiable genetic complement regulatory factor mutations or auto-antibodies to Factor H. Observational long-term follow-up data collection is on-going (C11-003). A retrospective study was also conducted to analyse data for both adults and children with aHUS who were treated with eculizumab outside these prospective trials.

In the two prospective aHUS eculizumab registration clinical trials and in the retrospective trial, eculizumab has shown considerable benefits in patients with aHUS. Interim data analysis in additional prospectively treated adult and paediatric aHUS patients demonstrates consistent efficacy and safety (C10-003 and C10-004); final data are not yet available for inclusion within this submission.

The eculizumab clinical trails have consistently shown that eculizumab causes significant gain of health for treated patients and has been demonstrated to:

- Inhibit complement activation in all treated patients;
- Inhibit complement-mediated TMA;
- Significantly improve renal function (including removal of dialysis);
- Prevent disease progression (including avoidance of dialysis);
- Eliminate need for burdensome PE/PI;
- Improve systemic organ function (including brain, gastrointestinal tract as described in the case reports below);
- Significantly improve Health-Related Quality of Life (HRQL); and
- Be well-tolerated (including experience in PNH patients for almost 10 years).

A multi-national registry has also been initiated to assess the long term manifestations of TMA complications and other clinical outcomes in aHUS patients, including eculizumab-treated or untreated patients. This aHUS Registry is active in the UK and has begun to recruit patients and will provide long-term follow-up data. All patients enrolled thus far in eculizumab clinical trials are eligible to enrol in a long-term, observational follow-up study (C11-003), after which time they will also be eligible to enter the aHUS registry.

Table A4 summarises the aHUS open-label studies performed to date and on-going studies. Studies are discussed in detail in Section C9.

Table A4: Summary of Eculizumab in aHUS Clinical Studies

Type of Study	Study Identifier	Study Objective	Study Design and Type of Control	Dosage Regimen, Route of Administration	Number of Treated Patients	Diagnosis	Duration of Treatment	Study Status Type of Report
Phase 2	C08-002A/B	Assess the safety and efficacy of eculizumab in patients with short-duration aHUS	Open-label, single arm	Eculizumab: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	17	aHUS	26 weeks; patients allowed to continue in long-term extension until product registered and available	Enrolment and primary endpoint complete; Clinical Study report complete; extension trial on-going; published report Legendre 2013
Phase 2	C08-003A/B	Assess the safety and efficacy of eculizumab in patients with a long duration of aHUS and chronic renal impairment	Open-label, single arm	Eculizumab: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	20	aHUS	26 weeks; patients allowed to continue in long-term extension until product registered and available	Enrolment and primary endpoint complete; Clinical Study report complete; extension trial on-going; published report Legendre 2013
Retrospective	C09-001r	Assess the efficacy and safety of eculizumab in aHUS patients treated outside of an Alexion-sponsored clinical trial	Retrospective, observational, non-interventional	Eculizumab; Variable dosing schedule	30	aHUS	Variable	Study complete; Clinical Study Report Complete

Type of Study	Study Identifier	Study Objective	Study Design and Type of Control	Dosage Regimen, Route of Administration	Number of Treated Patients	Diagnosis	Duration of Treatment	Study Status Type of Report
Phase 2	C10-003	Assess safety and efficacy of eculizumab in paediatric aHUS patients	Open-label, single arm	Eculizumab; Multiple weight-based dosing regimens.	22	aHUS	26 weeks; patients allowed to continue in extension until product registered and available	Enrolment and primary endpoint complete; [redacted]
Phase 2	C10-004	Assess safety and efficacy of eculizumab in adult aHUS patients	Open-label, single arm	Eculizumab: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	41	aHUS	26 weeks; patients allowed to continue in extension until product registered and available	Enrolment and primary endpoint complete; [redacted]
Observa tional	C11-003	Assess long term safety and efficacy in aHUS patients who previously participated in clinical studies [redacted]	Observatio nal	[redacted]	Data not yet available	aHUS	On-going	On-going
Registry	M11-001	Observational, non-interventional, multi-centre, multi-national study of patients with aHUS	Observatio nal	[redacted]	Data not yet available	aHUS	On-going; no analysis available	On-going; baseline abstract submitted

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

It is anticipated that the All Wales Medicines Strategy Group (AWMSG) will require a submission for eculizumab in aHUS despite NICE evaluation and guidance. The timing for this submission is not yet clear; however, we would expect an outcome in a timeframe similar to the NICE outcome.

The Scottish Medicines Consortium (SMC) also has requested a submission be made following grant of Marketing Authorisation.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Nothing in this submission would have an impact on equality issues.

5.2 How will the submission address these issues and any equality issues raised in the scope?

N/A because the submission will not have an impact on equality issues.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Overview of atypical Haemolytic Uraemic Syndrome (aHUS)

Atypical Haemolytic Uraemic Syndrome (aHUS) is a devastating, progressive, life-threatening, and ultra-rare disease caused by chronic uncontrolled complement activation. The disease affects both children and adults and has a very poor prognosis, demonstrated by the fact that 33% to 40% of aHUS patients die or progress to end-stage renal failure (ESRF) requiring dialysis with the first clinical manifestation.(Caprioli et al, 2006; Noris et al, 2010) The chronic nature of aHUS results in progressive, on-going morbidity as 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on plasma exchange or plasma infusion (PE/PI) or dialysis and a progressive increased mortality rate thereafter. Long-term data have shown a mortality rate of 32% at 4.4 years median follow-up.(Hovinga et al, 2010) The significant morbidity and mortality associated with aHUS represents an unmet medical need for patients with an ultra-rare and life-threatening disorder.

The complement system normally functions to defend against infections and is tightly regulated in order to limit excessive inflammation and organ damage.(Zipfel and Skerka, 2009) Patients with aHUS have one or more genetic mutations (although the mutation(s) are frequently not identifiable), causing deficiency in complement inhibitors or regulators. Chronic uncontrolled complement activation causes on-going platelet, endothelial, and white blood cell activation, leading to inflammation and thromboses (blood clots) in small blood vessels throughout the body, a process known as systemic thrombotic microangiopathy or systemic thrombotic microangiopathy (TMA).(Noris and Remuzzi, 2009; Karpman et al, 2006; Stahl et al, 2008; Stahl et al, 2011) Due to this on-going systemic TMA, aHUS patients are at constant risk of sudden and progressive damage and failure of multiple vital organs including the kidneys, brain, heart, lungs and organs of the gastrointestinal system, any and all of the failure of which can ultimately lead to severe morbidity and premature death.(Noris et al, 2010; Sellier-Leclerc et al, 2007; Neuhaus et al, 1997; Noris and Remuzzi, 2009) In studies that closely reviewed patient medical histories, TMA has been shown to result in a wide spectrum of extra renal complications, with reports of up to 53% of patients with neurological complications, 48% with cerebral convulsions, 43% with cardiomyopathy, 71% with hypertension, 12% with heart failure and 25% with clinical evidence of pancreatitis or diabetes.(Neuhaus et al, 1997; Vesely et al, 2003; Constantinescu et al, 2004) Of course, this does not take into account the total number of patients affected by any complication or with multiple complications.

Historical management of aHUS has been limited to supportive care including plasma exchange/ plasma infusion (PE/PI), chronic dialysis, or kidney transplantation, none of which positively impact the mortality of morbidity of aHUS or target chronic uncontrolled complement activation. These supportive care options for

aHUS patients are clinically inadequate, life-disrupting, and also pose significant safety risks for patients, with particular safety issues arising in children.(Michon et al, 2007; George et al, 2008; Noris and Remuzzi, 2009)

Dialysis does not address the underlying complement activation or systemic organ damage observed in aHUS patients, including those who are receiving dialysis; evidence of on-going TMA is observed in aHUS patients receiving dialysis.(Donne et al, 2002; Larakeb et al, 2007; Davin et al, 2010) Prior to eculizumab, few aHUS patients were offered the opportunity of kidney transplantation due to the extremely high rate of early graft loss, meaning they were effectively confined to long-term dialysis and its associated high mortality and morbidity. Following kidney transplantation, the on-going nature of the life-long uncontrolled chronic complement activation in aHUS causes graft loss in 66% of children and 55% in adults, as well as continued inflammatory and TMA insult to other organs.(Loirat et al, 2008; Noris et al, 2010)

Eculizumab directly and potently blocks activation of the terminal stage of the complement system, thereby inhibiting chronic uncontrolled complement activity, inflammation, and resulting systemic TMA, effectively reducing the underlying TMA process in aHUS patients, and allowing for clinically significant reversal or prevention of further kidney damage. As a result, some aHUS patients are able to discontinue dialysis and the majority of others treated early are able to avoid dialysis, kidney transplantation, and exposure to PE/PI. Eculizumab also prevents progression of other organ damage in aHUS patients and dramatically improves patients' quality of life.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011) The clinical benefits of eculizumab treatment reduce the public burden of disease, highlighting the value to society, as demonstrated further throughout the document.

Consequences of Chronic Uncontrolled Complement Activation in aHUS

The chronic uncontrolled complement activation present in all patients with aHUS directly leads to on-going systemic endothelial damage, platelet and leukocyte activation, micro-vascular damage, and ischemia in multiple organs. The consequences include sudden and progressive renal impairment and eventual ESRF as well as severe neurological, cardiovascular, and gastrointestinal complications.(Noris and Remuzzi, 2009; Noris et al, 2010) Overall, these manifestations can lead to a markedly shortened life-span for aHUS patients as well as a markedly impaired quality of life.

Although aHUS patients may not overtly exhibit clinical symptoms at all times, continuous and on-going damage to small vessels throughout the body due to the unremitting uncontrolled complement activation leads to chronic platelet and endothelial activation, which causes aHUS patients to be at constant risk of developing the more obvious and threatening clinical complications of the disease.(Holers, 2008; Noris and Remuzzi, 2009; Zipfel and Skerka, 2009) The more severe complications of aHUS often present with a suddenness that belies the underlying chronicity of the disease.

<u>Renal Complications: Renal Damage and End-Stage Renal Failure (ESRF)</u>

In a large cohort of aHUS patients, 32% were shown to progress to ESRF requiring dialysis within the first year of diagnosis.(Noris et al, 2010; Caprioli et al, 2006) Within three years of clinical manifestation, 65% of aHUS patients experienced permanent renal impairment or ESRF.(Noris et al, 2010; Caprioli et al, 2006) aHUS

patients who reach ESRF are consigned to life-long dialysis, which is associated with significant morbidity and mortality, since renal transplantation is rarely performed in these patients due to a 60% failure rate within one year, stemming from continuation of the underlying disease process.(Noris et al, 2010) Furthermore, in aHUS patients, dialysis does not reduce, and in fact has no impact on complement activation and its clinical sequelae.(Donne et al, 2002; Larakeb et al, 2007; Davin et al, 2010)

The risk of on-going complement-mediated TMA in patients with aHUS undergoing dialysis is in addition to the generally poor survival rates observed in dialysis patients. The overall five-year survival rate for dialysis patients (both those with aHUS and with other diseases) in 2004 in the United States and Europe was only 35% to 39%, illustrating the poor long-term outcomes associated with dialysis.(Collins et al, 2010)

Non-Renal End-Organ Complications

Chronic, uncontrolled complement activation leads to thrombotic events in the microvasculature throughout the body.(Benz and Amann, 2010) While renal impairment and ESRF are most commonly recognised as severe complications in aHUS patients, significant non-renal morbidity also occurs, affecting other vital organs, including the brain, heart, lungs, and gastrointestinal organs.(Hosler et al, 2003; Noris et al, 2010)

Specifically, in the retrospective eculizumab study C09-001r (described in detail below), 63% of patients had evidence of extra-renal organ involvement.(Langman, 2012; Alexion, 2012) While 100% of patients with aHUS have evidence of microvascular thrombosis as indicated by TMA, the highly pro-thrombotic nature of aHUS was further underscored by 37% of patients (11/30) experiencing extra-renal large vessel thromboses in addition to the renal impairment. Major large vessel thromboses noted in this study included stroke, transient ischaemic attack, myocardial infarction, splenic vein occlusion, pulmonary embolism, and deep vein thrombosis.

Neurological Complications

Neurologic complications have been reported in the literature in up to 48% of aHUS patients.(Neuhaus et al, 1997; Hosler et al, 2003) Complications reported include cerebral convulsion, cerebral infarction, stroke, confusion, impaired consciousness, and seizure, as well as fluctuating focal signs, such as motor deficits, diplopia, or aphasia.(Neuhaus et al, 1997; Hosler et al, 2003; Constantinescu et al, 2004; Noris et al, 2010)

Cardiac Complications

Cardiac complications in up to 43% of aHUS patients have been reported in the literature. These include cardiomyopathy, myocarditis, myocardial infarction, severe hypertension, and diffuse atherosclerosis.(Neuhaus et al, 1997; Sallee et al, 2010; Kose et al, 2010; Davin et al, 2010; Noris et al, 2010)

Gastrointestinal Complications

aHUS patients have also been reported in the literature to demonstrate signs or pathological evidence of pancreatitis, adrenal involvement, gastroenteritis, pancolitis, ischaemic colitis, hepatitis, and/or hepatic impairment.(Neuhaus et al, 1997; Noris et al, 2005; Davin et al, 2010) Diarrhoea is a presenting symptom in 30% of aHUS patients.(Zuber et al, 2011)

Impaired Quality of Life

aHUS patients suffer from multiple morbidities due to lifelong uncontrolled complement activation. These morbidities lead to an impaired quality of life as a result of the following symptoms:

- Central Nervous System (CNS) symptoms including as confusion, seizures, motor weakness, and focal signs;(Neuhaus et al, 1997; Vesely et al, 2003; Noris et al, 2010)
- Gastrointestinal (GI) symptoms including nausea, vomiting, diarrhoea, and pain;(Neuhaus et al, 1997)
- Cardiac symptoms including chest pain, dyspnoea;(Neuhaus et al, 1997; Constantinescu et al, 2004)
- Pulmonary symptoms including dyspnoea;(Loirat et al, 2010) and
- Impaired activities of daily living and quality of life.(Legendre et al, 2010; Muus P et al, 2010; Greenbaum et al, 2011; Licht et al, 2011)

aHUS patients are further burdened with cumbersome supportive care measures such as PE/PI and dialysis. Overall, patients on dialysis can expect shorter life expectancy and poor quality of life.(United States Renal Data System, 2011; European Renal Association, 2011)

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

As expected with an ultra-rare disease, data on the prevalence of aHUS are extremely limited. An estimate of the prevalence of aHUS in England is 5.5 persons per million, which is based on the prevalence of aHUS reported in NHS North East, specifically in the Newcastle area as reported by Professor Tim Goodship in a previous submission to the Advisory Group for National Specialised Services (AGNSS) in 2012. Additionally, no published data exist on the breakdown of adult vs. paediatric prevalence of aHUS. Based on our current market knowledge, and the wide age spread of patients with aHUS observed in the eculizumab clinical trials, we assume the probability of an aHUS clinical manifestation is equally likely to occur in children and adults.

Our base case incidence estimate for persons with aHUS is 0.6 persons per million, which is an assumption based on data received from the paediatric and adult renal units in the UK for prevalent and incident patients in 2009 to 2010 (data provided by Professor Tim Goodship, 2012), and projected to reflect recent data from English aHUS cases newly diagnosed in 2013. According to aHUS clinical experts in the UK, there is still some uncertainty that all cases of aHUS have been identified and diagnosed within England.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Data specific to the life expectancy of people with aHUS in England do not exist. However, information is available about the life expectancy, and likelihood of progression to ESRF, of people with aHUS from international cohorts.

Prior to the availability of eculizumab, the evidence from multicentre international HUS/TTP registry (including 73% from European countries), indicates that aHUS patients lose kidney function and progress to ESRF at high rates. Specifically, aHUS is a progressive and life-threatening disease with 33% to 40% of patients, the majority of whom received plasma exchange/infusion, reaching ESRF or death following the diagnosis of aHUS.(Caprioli et al, 2006; Noris et al, 2010)

Caprioli et al (2006) reported approximately 33% of patients reach ESRF or die following the first clinical presentation of TMA, and Noris et al (CJASN 2010) reported approximately 56% of patients reach ESRF or die at 3 years. (Caprioli et al, 2006; Noris et al, 2010) Fremeaux-Bacchi et al (2013) report 56% of adults and 29% of children require renal replacement or die within 1 year of follow-up.(Fremeaux-Bacchi et al, 2013) They report the Kaplan-Meier estimate of 5-year survival without ESRF was 64% in children compared with 36% in adults. Additionally, the survival of all patients who progress to ESRF and require dialysis is very poor. As reported in the UK Renal Registry 15th Annual Report (2012) Chapter 5 entitled "Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011", one-year age-adjusted survival for prevalent dialysis patients in the UK is 89.8%.(Steenkamp et al, 2012)

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

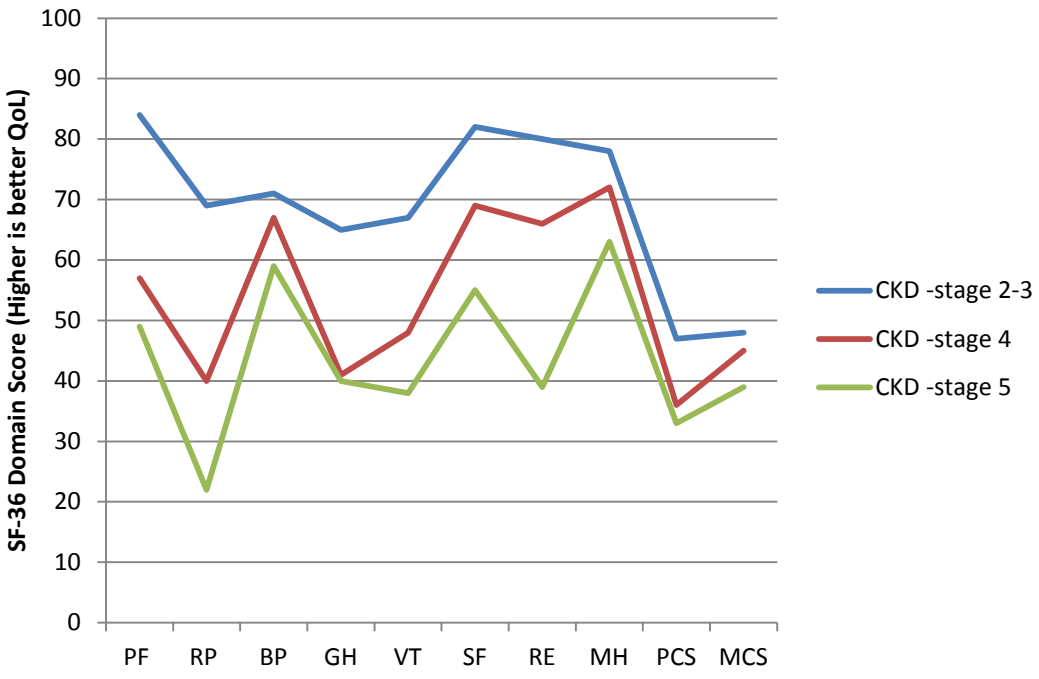
Drivers of Quality of Life (QoL) Impairment in aHUS

Disease morbidity

As described in Section 6, patients with aHUS suffer multiple morbidities that have a detrimental effect on their lives, and on the lives of those who love and care for them. The primary manifestation of the disease is on patient kidney function, such that up to 65% of all patients have been shown to die, require dialysis or have permanent renal damage within the first year of the diagnosis.(Caprioli et al, 2006)

Even in the absence of the other morbidities inflicted by aHUS, kidney disease is known to have a significant negative impact on patient quality of life.(Soni et al, 2010) This impact is associated with worsening kidney functioning. A Swedish study of chronic kidney disease (CKD) patients which assessed quality of life using the Short Form-36 (SF-36) questionnaire, found that all instrument domains deteriorated with CKD stage, with the lowest scores in CKD 5 (Figure B1). Role physical and General Health domains were particularly affected in CKD patients.(Pagels et al, 2012)

Figure B1: SF-36 Domains and Summary Scores in Different Stages of Chronic Kidney Disease



PF = Physical functioning, RP = Role physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role emotional, MH = Mental health, PCS = Physical summary scores, MCS = Mental summary scores.
Source: Pagels et al. 2012.

While kidney damage is the most recognised form of organ injury caused by aHUS, the disease causes multiple morbidities due to uncontrolled complement activation. These morbidities also lead to an impaired quality of life including the following symptoms:

- Central Nervous System (CNS) symptoms including confusion, seizures, motor weakness, and focal signs;(Neuhaus et al, 1997; Vesely et al, 2003; Noris et al, 2010)
- Gastrointestinal (GI) symptoms including nausea, vomiting, diarrhoea and pain;(Neuhaus et al, 1997),
- Cardiac symptoms including chest pain, dyspnoea;(Neuhaus et al, 1997; Constantinescu et al, 2004).
- Pulmonary symptoms including dyspnoea;(Loirat et al, 2010)

These symptoms are recognised to be associated with significant impact on patient quality of life and impairment in daily activities.(Legendre et al, 2010; Muus P et al, 2010; Greenbaum et al, 2011; Licht et al, 2011; Legendre et al, 2013) Whilst there is no aHUS specific data on the quality of life impairment associated with these morbidities, they have been shown to have a negative effect on quality of life among patients in other diseases.

Gastrointestinal symptoms significantly lower quality of life, with a linear relationship between the severity of the symptoms and the magnitude of the quality of life impairment.(Bovenschen et al, 2004) Cardiovascular disease has well recognised effects on quality of life. For example, the incidence of angina is predictive of a significantly worse emotional, physical, and social quality of life and a higher level of

depression.(Gravely-Witte et al, 2007) Dyspnea is strongly associated with impaired quality of life in conditions such as coronary artery disease and systemic sclerosis and affects patient sleep, appetite, communication and mood.(Khanna et al, 2005; Mohangoo et al, 2005; Arnold et al, 2009)

Standard of Care Treatment Impact on QoL

In addition to the quality of life impairment associated with the grievous symptoms of the disease, aHUS patients' lives are also impacted significantly by the misery related to ineffective supportive care measures, and specifically, PE/PI and dialysis.

Feedback from interviews with UK aHUS experts suggests that one of the major drivers of low quality of life in patients with aHUS is the requirement for frequent sessions of PE/PI. Patients may receive PE/PI as frequently as daily, and each session can last up to three hours. Patients are usually unable to perform normal daily activities after treatment.(Macmillan Cancer Support, 2013)

The side effects associated with PE/PI are described in Section 6 of this submission. Even in the absence of side effects, PE is physically gruelling and patients experience numbness, faintness, and post treatment.(Macmillan Cancer Support, 2013) As well as the physical burden, patients can also experience psychological trauma. A UK aHUS expert interviewed as part of this submission described a teenage aHUS patient who had previously been undergoing PE before receiving eculizumab. The expert said the patients biggest fear about his disease relapsing was the resumption of PE, about which he had extremely negative memories.

In interviews, UK aHUS experts thought that the large improvement in quality of life seen in the eculizumab trials could partly be explained by the removal of the need for patients to undergo plasma exchange.(Muus et al, 2011)

In the absence of treatment with eculizumab, many patients with aHUS will ultimately suffer from ESRF and require dialysis. Haemodialysis treatment requires patients to undergo three sessions per week, each lasting four hours. Both the process of receiving dialysis and the physical impact have negative implications for patient quality of life, not least the constrained potential for work or study due to the time requirements of dialysis. A meta-analysis of utility based quality of life measures in CKD found that dialysis patients had lower quality of life vs. pre-dialysis patients and patients who had received transplants.(Wyld et al, 2012)

In aHUS, dialysis can be expected to have a greater negative impact on patients' quality of life because the patient population is considerably younger than a normal dialysis population and they are less likely to have the co-morbidities that constrain activities a non-aHUS population. Accordingly, the restrictions imposed by dialysis are likely to be more burdensome in an aHUS population. This has been observed in the non aHUS literature, where significantly lower quality of life scores have been observed in patients receiving dialysis who are under the age of 65 versus older patients.(Avramovic and Stefanovic, 2012)

Both PE/PI and dialysis result in a substantial burden on informal carers and families of aHUS patients, particularly parents of children with aHUS. This burden is described in more detail in the following section.

UK aHUS Patient Survey

Results from the systematic literature review identified no observational studies reporting quality of life data in aHUS cohorts not treated with eculizumab. Therefore, in order to better understand the impact of aHUS on patients and their families, Alexion sponsored a survey of UK aHUS patients facilitated by the UK aHUS Patients and Families Support Group (aHUSUK). Members of the UK aHUS patient association were invited to complete an online questionnaire between August 7th and 21st, 2013. The survey contained questions concerning the impact of aHUS on the lives of patients and carers.

The surveys were completed by the patients themselves, except where the patient was a child, in which case responses were completed on their behalf by a parent or carer. In addition, some questions concerned the impact of aHUS on informal carers/caregivers which were to be answered by the primary carer, or, if not available, on their behalf by the patient. Respondents and their carers were asked to score how much aHUS impacted their daily activities including school or work, non-work, and leisure activities.

Please note: respondents to the questionnaire did not have to answer every question if they did not wish. Therefore, the sample size varies between items. Sometimes patients answered one question in a certain domain, but not another, and therefore for some domains (such as support from carers), the denominators for statistics might vary.

Thirty-seven patients with aHUS completed the survey. Sixty-two percent of respondents were female (n=23) and 34% were under the age of 18 (n=12). The average age of patients was 29 years (n=37). Most respondents (n=14) had been diagnosed within two to five years and had last attended hospital for aHUS treatment within the month prior to responding to the survey (n=18). Of those respondents aware of their kidney disease staging (n=18), 50% were in an advanced stage/ESRF (n=9).

It is important to note that nearly half of the patients in the sample (17/37) were already receiving eculizumab, and therefore the quality of life reported is not reflective of a population only receiving standard of care treatment.

<u>Patient QoL impact</u>

Patients were asked to score the extent that aHUS impacts their day-to-day activities on a scale of 0 (no effect on activities) to 10 (activities completely prevented). Activities were defined as work/school, non-work (i.e. housework, shopping, childcare, exercising, studying, etc.), and leisure activities.

Impact on Productivity and Education

Patients reported a significant impact of aHUS on productivity, with a mean score of 6.7 (range 2-10; n=21). Patients under 18 years of age (n=7) reported a greater impact on productivity with an average score of 7.3 (range 2-10). Furthermore, 83% (5/6) of patients under 18 (n=6) reported that aHUS had negatively impacted their education.

Forty percent (9/23) of adults with aHUS (n=23) reported that they were not currently in employment (average age 29 years), with 50% (4/8) of these either on sick leave (n=2) or unable to work because of their disease (n=2). The remaining 50% (4/8) were either retired (n=3) or job seeking (n=1). Fifty percent (10/19) of adult patients

with aHUS reported that their income had been reduced as a result of their disease (n=10).

Impact on Day-to-Day Activities

Patients were asked to score how much aHUS impacted their regular non-work activities (defined as housework, shopping, childcare, exercising, studying, etc.), how they were limited in the amount or kind of activities they could usually do, and how many times they had accomplished less than they would like due to aHUS.

Patients (n=27) reported a substantial impact on daily activities, with a mean score of 5.1, (where 0 indicated "no effect on activities" and 10 indicated "activities completely prevented) with similar scores for children (score 4.7; n-9) and adults (score 5.3; n=18).

Impact on Leisure Activities

A similar level of impact (mean 5.0) was seen when patients (n=27) were asked about the impact of their disease on leisure activities. Amongst adults (n=18), 23% (4/18) of respondents reported that aHUS had completely prevented participation in leisure activities (n=4).

Lifestyle Adaptation

Twenty-nine percent (8/28) of patients stated that they had had to move house as a result of their disease (n=8). Reasons provided for moving included being closer to a specialist centre (n=1), closer to a relative or carer (n=1), or in a more suitable type of accommodation (n=4). On average, patients with aHUS have to spend 4 hours travelling each week for activities associated with their aHUS (such as hospital visits) (n=5). When the patient is a child, then a parent or carer usually must provide transportation and accompany them, adding to the burden.

Overall Patient Quality of Life

Patients were asked to score their overall quality of life on a numerical rating scale using a question similar to that used in the European Quality of Life - Group 5 Dimensions Self-Report Questionnaire (EQ-5D) ("*Please indicate how you assess your overall health status by circling a number on the scale below, where 0 equals the worst imaginable health state and 10 equals the best imaginable health state*").

Patients (n=25) reported an overall score of 6.4, with patients under 18 years (n=10) having a slightly better quality of life (6.7 in adults vs. 6.2 in patients under 18 years).

<u>Families and Carer QoL impact</u>

Fifty four percent of patients (20/37) reported that they received help from an informal carer. In response to a separate question answered by the carers, (n=9), the average time spent looking after a patient with aHUS was 44 hours. Where care was provided informally the relationship between the carer and patient was that of spouse in 31% (5/16) of cases, other relatives in 69% (11/16) of cases (note: not all patients with informal carers answered this question).

Seventy-five percent (15/20) of informal carers (n=20) reported that they had to reduce their work activities in order to provide care, with an average reduction in working hours of 17.9 hours per week (n=13).

Almost all informal carers (19/20) reported feelings of tiredness and stress associated with their responsibilities. The proportion of carers responding '*a lot of the time*' or '*always*' to the following questions were:

- "*I feel worn out as a result of caring*": 32% (6/19) (n=1 "always" and n=5 "a lot of the time");
- "*I feel stressed as a result of caring":* 44% (8/18) (n=3 "always" and n=5 "a lot of the time"); and
- "*I feel mentally exhausted by caring*": 32% (6/19) (n=0 "always" and n=6 "a lot of the time").

<u>Direct statements about aHUS burden from patients and their families</u>

The findings from the aHUS patients' survey are illustrated below by quotes from patients and families of patients with aHUS:

- "*A devastating and terrifying experience...it took a while to gather strength to fight it*."

- "*Shocking! The whole illness came without warning and was life threatening within a few days. The greatest problem was not knowing what was wrong*."

- "*aHUS changed my life irrevocably*."

- "*It has been the hardest thing I have ever had to deal with*."

- "*The condition has not only affected us as her parents, but also her grandparents and aunts and uncles, it really does change your life forever. When we decided to have children, we did not ever imagine having to see our child so sick.*"

- "*We have been devastated by this condition. The way it has affected our family is quite frightening.*"

- "*It has taken over our life*."

Many family members of patients with aHUS shared particularly distressing experiences of caring for – and in some cases losing – children with aHUS, and how multiple members of their family had been affected by the disease over several generations. The following quotes were captured during the survey:

- *"Our child became sick when he was just five months old in 1974 and he was eventually diagnosed. He died at seven months. Two years later we experienced the same again and we lost another little boy. We had questioned the hereditary factor but at that time no one knew anything. In the 1990s I was one that was tested to identify the gene. We had a great niece diagnosed in 2005 and her younger brother a couple of years later. We have had our grandson diagnosed this year. These young children have had on-going therapy with plasma exchange. Over the years, we have lost an uncle and cousins, which on reflection were from aHUS."*

- "*aHUS was diagnosed in our son when he was 13 months following a cold-like infection. His older brother had died from the disease so we recognised*

the symptoms and insisted on a referral to a paediatrician. [Patient] died during his third relapse when he was 17 months."

- "*Having a child with aHUS in the family is overwhelming and a constant worry. The whole family is affected due to long hospital stays and the pressure of not knowing when the disease will strike next*."

- "*Our baby died when he was only four months of age. He had cold-like symptoms for 48 hours previous to being treated at the hospital where he died within a few hours*."

The Financial Implications of aHUS

aHUS can cause severe financial problems for patients and their families. As aHUS is such a serious disease, and patients are unable to work during its acute stages, many family members give up work to care for them. Giving up work to provide care had a crippling effect on their finances. Below are some of the quotes related to the financial aspect of this disease:

- "*It affected us financially to the point where we nearly lost our home because my husband was the only person earning money and we had a mortgage to pay*."

- "*I had to give up work as my employer was not very supportive*."

- "*aHUS has totally changed our family. I had to give up work to care for our daughter. As her condition is so unpredictable I was being called away from work so often to take her to hospital, where we have open access, I felt I could no longer commit to my employer. This has obviously had a huge financial impact on my family*."

Recent Newspaper Articles Summarising Experiences for Patients with aHUS

Two recent newspaper articles were published in the UK that provides further insights about patients living with aHUS:

- Article entitled "*Newcastle breakthrough over kidney disease*". Published in the Evening Chronicle on January 10, 2012. Available online at http://www.chroniclelive.co.uk/north-east-news/evening-chronicle-news/2012/01/10/newcastle-breakthrough-over-kidney-disease-72703-30092531/;

- Article entitled "*Patient with deadly kidney disease hails wonder drug that could halt disease which killed seven family members*" Published in the Daily Mail on January 10, 2012. Available online at http://www.dailymail.co.uk/health/article-2084750/aHUS-Patient-deadly-kidney-disease-hails-wonder-drug-halt-disease.html?ito=feeds-newsxml.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or

quantity of life of particular group(s) of patients, and their families or carers.

In the two prospective aHUS eculizumab clinical trials and a retrospective trial, eculizumab has shown considerable benefits in patients with aHUS. Specifically, eculizumab has been demonstrated to:

- Inhibit complement activation in all treated patients;
- Inhibit complement-mediated TMA;
- Significantly improve renal function (including removal of dialysis);
- Prevent disease progression (including avoidance of dialysis);
- Eliminate need for burdensome PE/PI;
- Improve systemic organ function (including brain, gastrointestinal tract as described in the case reports below);
- Significantly improve HRQL; and
- Be well-tolerated (including experience in paroxysmal nocturnal haemoglobinuria (PNH) patients for almost 10 years).

The eculizumab clinical trial data are discussed in detail in Section 6 of this submission.

To further illustrate the impact providing eculizumab has on patients with aHUS, the following illustrative information is provided below:

- References to published case reports;
- Quotes from patients and their families on the benefit of having access to eculizumab

aHUS Case Reports

Short summaries of four published aHUS cases are described below. Case 1 illustrates the progressive course of aHUS and eventual development of organ failure (neurological, renal, and widespread arterial disease) that most frequently results despite the use of PE/PI, but without eculizumab intervention. Cases 2 through 4 highlight the significant benefit of eculizumab in reversing systemic organ damage and preventing disease recurrence.

<u>Case 1: Loirat 2010</u>
Reference: Loirat C, Macher M-A, Elmaleh-Berges M et al (2010) NDT25 (10): 3421-3425.

A female patient was diagnosed with aHUS at one month of age and began haemodialysis at four months. She underwent bilateral nephrectomy at one year due to hypertension, persistent haemolysis and thrombocytopaenia (evidence of complement-mediated TMA). She received a cadaveric transplant at age 19 months. Evidence of TMA and graft failure was seen 15 days post-transplant and despite the use of plasma exchange no clinical improvement was noted. With on-going plasma exchange and IV immunoglobulin, kidney function was lost. The patient resumed dialysis at age 6 years and nephrectomy of the graft was performed. At age 10 years, the patient began to have spontaneous episodes of hemiparesis bilaterally associated with losses of consciousness. Vascular imaging revealed bilateral stenosis of the carotid and cerebral arteries. At age 12 years CT thorax, cardiac catheterisation and angiogram showed stenosis of all branches of the pulmonary arteries as well as pulmonary hypertension and coronary artery stenosis. At age 13

years the patient developed visuo-spatial apraxia. She was placed on the kidney transplant list, which was planned to be conducted with eculizumab treatment. Pre-operatively it was necessary to perform recanalisation of the right internal carotid artery to restore cerebral blood flow. The attempt to perform angioplasty was complicated by dissection which led to massive hemispheric infarction and cerebral oedema resistant to craniotomy. The patient died four days later.

Case 2: Davin 2010
Reference: Davin JC, Butler N, Grootnoff J et al (2009) Pediatr Nephrol 24: 1757-1760

A child presented with features of aHUS at the age of three years. Renal function was rapidly lost and she commenced peritoneal dialysis. She received a cadaveric renal allograft at age five years. Three days post-operatively, TMA was observed. A graft nephrectomy was undertaken. At age 12, the patient received a second renal transplant. She received pre- and post-operatively plasma exchange and the initial post-operative course appeared uncomplicated. Good graft function was established and continued until eight weeks post-operatively when frequency of PE was reduced from weekly to every two weeks. Ten weeks post-transplant, serum creatinine increased. Due to the high clinical suspicion of graft rejection, she received methylprednisolone. Creatinine continued to increase. Transplant biopsy was performed and revealed thrombotic microangiopathy. Intensive PE did not prevent loss of the graft several days later. Haemodialysis was re-initiated. At age 15 years, the patient developed neurological symptoms. Magnetic Resonance Imaging (MRI) showed severe cerebral artery stenosis. At the age of 17 years, a third transplant was performed using pre- and post-operative PE. Post-operatively the patient developed right frontal infarcts manifesting as left-sided hemiparesis, focal seizures and impaired consciousness. She made a progressive recovery. PE was administered regularly but four months post-transplant an increase in serum creatinine was observed, accompanied by haemolysis and thrombocytopaenia. Daily PE was administered. Ten months post-transplant, serum creatinine levels were elevated but stable. At this time, the patient began to develop increasingly frequent allergic reactions of considerable severity to plasma exchange. Despite prophylactic steroids and anti-histamines prior to PE, hypotension and respiratory distress induced by PE necessitated the use of adrenaline. PE was eventually discontinued in view of the potential cerebrovascular risk associated with the procedure. At this time, eculizumab was started and continued as a chronic therapy. No adverse reactions were noted and six months after starting treatment (at the time of publication of this case report), creatinine levels were stable, there was no significant change in haemoglobin, lactate dehydrogenase (LDH), haptoglobin levels and platelet count were normal.

This case illustrates the progressive and systemic nature of aHUS and the loss of kidney transplant function that will inevitably occur due to on-going complement-mediated TMA, despite the use of PE. It also illustrates the burden and safety issues associated with PE. Eculizumab use, even in this advanced disease setting, was able to prevent TMA and preserve remaining organ function.

Case 3: Ohanian 2011
Reference: Ohanian, M. Clin Pharm Adv and Applications; 2011; 3-5.

A 50 year-old female patient was admitted to intensive care with sepsis, acute renal failure, pancolitis and thrombocytopaenia. Laboratory investigations showed an elevated creatinine, low platelet count, increased LDH and low haptoglobin; all consistent with TMA. The severe gastrointestinal symptoms necessitated total

colectomy with end ileostomy on admission. The pathology report showed damage consistent with microangiopathy. Mental and respiratory decline ensued; the patient remained intubated and became unresponsive and developed seizures. Renal failure worsened and haemodialysis was initiated on day 4. The patient was diagnosed with aHUS. On day six, eculizumab treatment was started and continued weekly for four weeks after which chronic therapy was maintained on a two-weekly basis. Four days after eculizumab initiation a reduction in LDH levels was observed. At seven days post-initiation of eculizumab the patient became responsive and at day 10, dialysis frequency was reduced to 3 times/week. At 11 days, the patient was weaned off the ventilator and within a few days no longer required oxygen. Just over three weeks after starting eculizumab therapy, renal improvement was noted and urinary output increased and dialysis was discontinued. The patient has remained off dialysis since. Two months post-first dose of eculizumab, LDH and haptoglobin levels were normal. MRI performed 26 days post-eculizumab treatment revealed a sub acute parietal infarction, however neurological stability was achieved and the patient had remained neurologically stable at the time of publication. She has remained off dialysis on long-term therapy and creatinine levels have continued to fall. This case illustrates that the use of chronic eculizumab therapy led to a reversal of neurological impairment and elimination of the need for dialysis.

Case 4: Duran 2011
Reference: Duran CE, Maduell F and Campistol JM (2012) NTD plus (with permission from authors).

A 28-year old man presented to the emergency department with renal insufficiency, elevated LDH, low platelets and low haptoglobin, and was diagnosed with aHUS. Intensive plasma exchange was initiated every two days for one month however no clinical improvement was observed. Chronic haemodialysis was then started. The patient experienced significant systemic symptoms, including severe dilated cardiomyopathy, alveolar haemorrhage, and thrombosis in the retina. Four years later the patient received a kidney transplant however required haemodialysis for 20 days due to delayed graft function. One month later, deterioration in renal function was noted by a markedly elevated serum creatinine. Blood tests and renal biopsy confirmed active TMA and intensive plasma exchange was initiated (every other day times eight sessions). Some improvement in haemolysis markers was observed however one month later, the patient was re-admitted with a markedly elevated serum creatinine, low haemoglobin, low platelet count and renal biopsy confirmed severe TMA. Chronic dialysis was started and eculizumab treatment was initiated. Two months post-initiation of eculizumab there was a marked improvement in renal function and a gradual reduction in need for dialysis. At 3.5 months after starting eculizumab therapy, dialysis was discontinued. The patient remained in good health over a 10-month follow-up period with on-going eculizumab treatment and no evidence of clinical manifestations of TMA was observed.

Quotes from patients and their families in support of a National Specialised Service for eculizumab in aHUS

The patients and families who responded to the aHUSUK patient survey were unanimous in their strong support for a national specialised service for aHUS, and were clear how much it would mean to them. The following quotes were captured describing their specific thoughts:

- "*Receiving treatment from a specialised aHUS service would mean that an illness that had such a devastating effect on my life would finally be dealt with instead of just the consequences of the illness*."

- "*It would mean knowing the best possible care was being given by world experts.*"

- "*It would give confidence that the right treatment is being given and also that new advances in the understanding and treatment would be readily available*."

- "*We are in no doubt that earlier diagnosis of aHUS and referral to a centre of excellence will make a significant difference to recovery rates*."

They were also unanimous in calling for the provision of eculizumab for all patients who need it, which some regarded as their only hope for the future, and expressed their grave concerns that the Government might choose not to make it available in the NHS.

- "*There is no current treatment for my wife's aHUS unless the drug eculizumab becomes available*."

- "*The future on eculizumab is so much brighter for me and will be for our sons if eculizumab becomes available on NHS*."

- "*It is hugely disturbing to know that a tested new drug can be used for the effective treatment of this condition but might not be available solely because of the expense of it*."

Two patients who had received eculizumab in a clinical trial outlined how it has significantly transformed their lives:

- "*My initial treatment was plasma exchange. In the beginning, I found daily plasma exchange very intrusive and exhausting. I suffered a variety of adverse reactions to the treatment, including sickness, sudden drop in blood pressure, anaphylactic shock, itching and hives. As I got stronger, I began to cope better but the adverse reactions continued and I needed to take an anti-histamine and another drug before every session. These made me very drowsy for the following 24 hours. In addition to this inconvenience there was always the risk of infection from the central line needed for plasma exchange. All this changed in August 2011 when I joined the clinical trial for eculizumab. I cannot believe the difference it has made in my life. The central line has been removed and infection risk reduced. The administration of the drug is by infusion once a fortnight and this lasts 35 minutes. The drug started to work almost immediately and there have been no side effects. I have become so much stronger and can now do much more. The incidents of fatigue have almost disappeared. My enthusiasm for life has returned. Every day I feel lucky that I am able to receive eculizumab.*"

- "*My husband has been able to resume his retirement activities and I have returned to a more independent life. Our lives are nearly back to normal thanks to eculizumab and the team at [hospital]*."

One of the many goals of the specialised service will be to enable successful kidney transplants in aHUS patients who already have kidney failure and are on dialysis. In most cases, without treatment with eculizumab, patients were told that they are not recommended to receive an organ transplant because a 50% to 80% risk exists of

the transplanted organ being lost within two years. Three patients' experiences of how TMA from aHUS had attacked their newly transplanted kidneys are shared below:

- "*I was very ill and at one point was given 24 hours to live. Luckily I pulled through with dialysis and plasma exchange. I was told my kidneys may start to work again within three months but if they didn't then I would be looking at a transplant. After my kidneys did not work again I was donated a kidney…unfortunately the aHUS came straight back and attacked the kidney.*"

- "*In 2005 I had a transplant….everything was OK for four months then the aHUS began attacking the transplanted kidney*."

- "*I had a transplant in 2006 which failed after two weeks due to the return of the aHUS so that was very sad as the donor who was my fiancé at the time left me due to the failure*."

The proposed service and treatment with eculizumab would ensure that this does not happen in the future.

<u>Impact of aHUS on Access to Kidney Transplants</u>

With the availability of eculizumab these patients would be able to receive a life-changing organ transplant. The possibility of an organ transplant gives them hope, and would change their lives by freeing them from dialysis. Below are some thoughts on this issue from patients:

- *"When I first heard about eculizumab I could hardly dare to dream it could be true. I spent 10 years thinking that I would be on dialysis for the rest of my life. I left Professor Goodship's office thinking there was a glimmer of light at the end of a very dark tunnel. That light is getting brighter so funding for a specialised service would make it shine through."*

- *"If a drug was available it would change our lives. My wife would be able to go back on the transplant list. We would love to have another baby and look to the future whilst my wife is still well but this is not an option without a specialist aHUS service where we can access new trials, medications, etc."*

- "*I would like to maintain my health on dialysis in order to return to the transplant list someday but this can only happen if the drug eculizumab is available to me.*"

- "*Being unable to have a transplant for the last decade has led to awkward conversations because a transplant is seen as the ultimate cure. I have had to explain many times that a transplant was not an option and each time it hurts as much as before to feel so hopeless.*"

- "*If I could receive eculizumab it would mean a chance of a transplant which could equal a new lease on life for me*."

The compelling clinical outcomes, the patient testimonies and benefits of availability of a homecare service for patients demonstrate the positive health and non-health benefits for patients on eculizumab treatment.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

NHS England has provided guidance through the Clinical Priorities Advisory Group (CPAG) evaluation of eculizumab that routine commissioning will be provided for:

- New patients with atypical haemolytic syndrome (defined to include those with a functioning kidney); and
- Existing patients who are on dialysis and are suitable for a kidney transplant.

A commissioning for evaluation scheme will be developed for patients who are not suitable for transplant.

the NHS England policy entitled "Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome was published on 11th September 2013. has not been made public and will be provided to the National Institute for Health and Care Excellence (NICE) once published. The policy itself provides for commissioning all aHUS patients with no separation of sub-groups, genotypes or age ranges. The commissioning for evaluation scheme provides coverage of patients on dialysis who may not be suitable for transplant yet suffer non-renal TMA events which could be treated with eculizumab. Thus, all diagnosed aHUS patients could have access to eculizumab treatment. Importantly, there is no restriction on the length of therapy, recognizing the fact that, per the Summary of Product Characteristics (SmPC) and European Medicines Agency (EMA) approval, treatment with eculizumab is recommended to continue for the patient's lifetime, unless the discontinuation of eculizumab is clinically indicated.

In 2009, clinical practice guidelines for aHUS were published on behalf of the Renal Association, the British Committee for Standards in Haematology, and the British Transplantation Society.(Taylor et al, 2010) These guidelines included recommendations for the investigation and management of aHUS patients in the UK prior to the availability of eculizumab for aHUS, for which clinical trials were underway at that time. These guidelines used the Grading Recommendations Assessment, Development, and Evaluation (GRADE) system to classify the strength of the recommendations as strong or weak and the quality of the evidence as high, moderate, low, or very low.(Gordon et al, 2008)(Table B1).

Table B1: GRADE system ratings for 2009 aHUS clinical practice guidelines

Investigation	**Recommendation**	**Grading** (Strength of recommendation, quality of evidence)
Measurement of serum complement	Serum levels of C3, C4, factor H, factor I	Strong, moderate
FACS analysis	Assessment of CD46 (MCP) expression on PBMC's	Strong, moderate
Genetic analysis	Mutation screening of Complement Factor H (CFH), CD46, CFI, CFB, and C3	Strong, moderate
Autoantibody screening	Screening for autoantibodies against factor H	Strong, moderate

Investigation	Recommendation	Grading (Strength of recommendation, quality of evidence)
Rare causes of aHUS	Consider rare forms and undertake appropriate investigations	Strong, moderate
A disintegrin and metalloproteinase with thrombospondin-1 motifs [13th member of the family] (ADAMTS13) activity	Measurement of ADAMTS13 activity; include assay for anti-ADAMTS13 antibodies if activity lower than 10%	Weak, low
Management	**Recommendation**	**Grading**
PE/PI	Trial of PE/PI	Weak, low
Kidney transplantation	Not recommended due to risk of aHUS after transplantation	Strong, moderate
Liver transplantation, combined liver/kidney transplantation	Considered in patients with known mutation in CFH or CFI	Weak, low

Investigation of aHUS

Although some of the investigations evaluated by Taylor et al received strong recommendations, it was not proven that the implementation of these investigations would result in improved outcomes for aHUS patients. Several limitations to these investigations were also noted in these guidelines. First, with regard to genetic analysis, the evidence cited by Taylor et al state that 40% of patients will not have a recognised mutation or antibody to the complement system. Additionally a significant proportion of aHUS patients do not have low C3 levels. The poor morbidity and mortality outcomes described in Taylor et al, 25% mortality and 50% progression to renal failure, and in other sources cited within this submission, are in cohorts including patients with and without genetic mutations and with and without altered complement protein levels. Therefore, genetic analysis as recommended by Taylor et al may not positively identify all patients that would appropriately be diagnosed with aHUS. Nor would genetic analysis have an impact on the assessment of patient management as follows:

- Despite the emphasis on identifying complement dysregulation, Taylor et al. 2010 acknowledges that genetic screening cannot be utilised to inform treatment decisions due to lengthy turnaround time of months. This is critical as 33% to 40% of patients die or have ESRF following diagnosis.(Caprioli 2006, Noris 2010) This conclusion is supported by clinical trials in which eculizumab was shown to have similar clinical benefit in aHUS patients regardless of identified mutation or no mutation.(Legendre et al, 2013)

- In the case of serum complement measurement, Taylor et al. state that C4 levels are normal in most cases, C3 levels may be normal or low in patients with identified mutations, and some patients without identified mutations may have low C3.(Caprioli et al, 2006; Kavanagh et al, 2006) Interpretation of factor H and factor I concentrations can be complicated by wide variability in the normal population. These limitations demonstrate that measurement of serum complement concentrations can lead to false-negatives and should not be used to diagnose or make treatment decisions in aHUS.

Measurement of ADAMTS13 activity should be undertaken in all patients with a clinical diagnosis of aHUS. As noted by Taylor et al., the understanding of the molecular mechanisms of thrombotic thrombocytopenic purpura (TTP) vs. aHUS mediated by severe ADAMTS13 deficiency and complement dysfunction respectively has greatly improved diagnostic differentiation compared to historic differentiation by clinical characteristics alone. While these guidelines characterised the evidence for ADAMTS13 measurement as weak, evidence linking TTP pathology to severe ADAMTS13 deficiency has continued to evolve since the publication of these guidelines. It is now clear that the von Willebrand factor-mediated platelet aggregation which mediates TMA in TTP cannot occur without severe deficiency of ADAMTS13 activity.(Tsai, 2013b) Recent guidelines from the British Committee for Standards in Haematology conclude that ADAMTS13 activity <5%, with or without the presences of inhibitor or IgG antibodies, confirms TTP diagnosis.(Scully et al, 2012) Accordingly, all patients included in eculizumab clinical trials had ADAMTS13 > 5%, as noted in both the SmPC and US Food and Drug Administration (FDA) prescribing information. Therefore, medical evidence demonstrates that patients with signs and symptoms of TMA but with ADAMTS13 activity ≥5% are diagnosed with aHUS. In absence of rapidly available ADAMTS13 activity test results, laboratory parameters can be used to identify patients with high suspicion of aHUS. When serum creatinine ≤200 µmol/L or platelet count ≤ 30,000/mm^3 are present, it is highly associated with absence of severe ADAMTS13 deficiency with a negative predictive value of 93.3% (95% CI 85.2-100%) minimizing false negative diagnosis.(Coppo et al, 2010; Zuber et al, 2012a)

Management of aHUS

The guidelines highlight the weak evidence around current supportive care including PE/PI to manage aHUS. At the time of this recommendation, it is highlighted that there is currently no specific therapy for aHUS.

The recommendations highlight that the use of PE/PI for aHUS is only empirical with limited therapeutic value or strategy. The use of PE/PI received weak recommendations with low quality of evidence to demonstrate utility or efficacy in the management of aHUS. Taylor et al 2009 also cite poor outcomes remaining in patients receiving PE/PI as supportive care, with an initial mortality of 25% and 50% renal failure rate in surviving patients and as cited by larger aHUS registries of 33-40% of patients progress to ESRF or die within 1 year of TMA prestation.(Schieppati et al, 1992; Taylor et al, 2004; Caprioli et al, 2006)

Lastly, although reported kidney or combined liver/kidney transplantation outcomes vary, risk of graft loss occurs in all aHUS patients regardless of identified complement mutation. Recommendations to avoid transplantation and inform patients of risks were graded as strong by Taylor et al 2009.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

No published NICE clinical pathway exists that is specific for aHUS. The following pathway might have some relevance in terms of early identification of kidney disease, but it is not specific to aHUS: Chronic Kidney Disease (CKD) pathway available at http://pathways.nice.org.uk/pathways/chronic-kidney-disease. This pathway covers the early identification and management of CKD in adults in primary and secondary care. It also includes a quality standard that covers the identification, assessment, and clinical management of CKD in adults including the management of

established renal failure, and other guidance produced on renal replacement therapy including transplantation and dialysis.

Overview of evidence for use of eculizumab in aHUS

Eculizumab is designed to directly and potently block activation of the terminal stage of the complement system.(Rother et al, 2007) As a result, use of eculizumab reduces the underlying systemic complemented-mediated TMA process and subsequently can reverse or prevent further kidney damage, which in turn has been shown to lead to a discontinuation or avoidance of dialysis. Eculizumab has also been shown to prevent progression of other organ damage in aHUS patients, and has demonstrated a reduction in the need for PE/PI and a significant improvement in patients' quality of life.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011; Alexion, 2012; Legendre et al, 2013) These benefits were demonstrated in two prospective controlled clinical trials and a retrospective analysis involving a broad range of aHUS patients of all ages.

When compared to the natural progression of the disease and historically poor outcomes at one year, these trials are the first to demonstrate the efficacy of a definitive, targeted treatment for aHUS patients.(Legendre et al, 2013; (Gruppo and Rother, 2009; Legendre et al, 2010; Muus P et al, 2010; Davin et al, 2010; Lapeyraque et al, 2011) Eculizumab treatment in aHUS patients was shown to change the course of the disease and to lead to substantial and demonstrable gains in patient health. In recognition of the chronic nature of aHUS and the on-going substantial risk of mortality and significant morbidities, the Soliris Summary of Product Characteristics (SmPC) states that eculizumab treatment is recommended to continue for the patient's lifetime.

Diagnosis and management of aHUS with eculizumab in England

aHUS patients present with signs of TMA, including one or more of the following: evidence of platelet consumption [as measured by low platelets (thrombocytopenia), or declining platelet count] and microangiopathic haemolysis [as measured by elevated LDH, low haptoglobin, or schistocytes], or biopsy-confirmed TMA. In addition to laboratory evidence, patients may develop clinical signs and symptoms of renal, gastrointestinal, neurological, and/or other organ complications. Patients presenting with acute renal failure (with or without evidence of other organ damage) are to be managed with renal replacement therapy as appropriate according to NICE pathways for acute kidney injury (http://pathways.nice.org.uk/pathways/acute-kidney-injury) or CKD (http://pathways.nice.org.uk/pathways/chronic-kidney-disease).

Clinical manifestation of aHUS can present with signs and symptoms similar to those of Shiga-toxin producing enterohaemorrhagic *Escherichia coli*-induced HUS (STEC-HUS) and severe ADAMTS13 deficiency (TTP). In patients presenting with the above signs of TMA and where there is suspicion of the differential diagnosis of either STEC-HUS or TTP, diagnostic tests should be rapidly undertaken to exclude these disorders. If patients present with bloody diarrhea and TMA, tests for shiga-toxin producing enterohaemorrhagic *Escherichia coli*-induced HUS (STEC-HUS) include assays for shiga toxin (Polymerase Chain Reaction (PCR) or immunoblot) or *E. coli* stool culture. Congenital or acquired TTP is defined by severe ADAMTS13 activity deficiency (<5% activity) with or without ADAMTS13 autoantibodies. In adult patients, serum creatinine > 150-200 µmol/L or platelet count > 30,000/mm^3 is highly indicative of aHUS, and exclusion of severe ADAMTS13 deficiency, when rapid confirmation by lack of severe ADAMTS13 deficiency cannot be obtained.(Coppo et al, 2010; Zuber et al, 2012a)

Patients with aHUS can present in the setting of other conditions or diseases that unmask aHUS including malignant hypertension, systemic lupus erythematosus, drug-induced TMA, Haemolysis, Elevated Liver Enzymes, Low Platelets (HELLP), or preeclampsia. These conditions can lead to increased complement activation, and unmask the underlying uncontrolled complement activation, in aHUS patients. Thus aHUS should not be ruled out in patients with these conditions.(Campistol et al, 2013) Presence of persistent or progressing TMA in these co-existing conditions should not rule out the diagnosis of aHUS or the need for eculizumab therapy to inhibit complement-mediated TMA.

Considering the medical evidence for efficacy of eculizumab to inhibit complement-mediated TMA and stabilise or improve organ function as described in Section 9, eculizumab should be utilised for first-line treatment in patients diagnosed with aHUS.(Zuber et al, 2012) PE/PI should not be utilised as first-line supportive care in these patients due to the lack of medical evidence demonstrating effect of PE/PI on complement-mediated TMA, renal survival or other outcomes in aHUS and due to the fact that delay in treatment with eculizumab may lead to permanent renal damage or on-going organ damage.(Zuber et al, 2012a; Legendre et al, 2013)

All patients diagnosed with aHUS as described above, with native or transplanted kidneys, should be treated with eculizumab therapy as follows to inhibit on-going and destructive complement-mediated TMA and resulting end-organ damage:

- First line treatment in all patients with aHUS at first presentation or subsequent admission.
- Patients on short-term dialysis or long-term dialysis who have evidence of TMA (e.g. including low or declining platelets, evidence of haemolysis such as elevated LDH, low haptoglobin, or presence of schistocytes) or extra-renal organ damage.
- Patients with aHUS-induced renal failure who are listed for renal transplant should be treated with eculizumab to prevent post-transplant complement-mediated damage and graft loss.(Zuber et al, 2012b; Zuber et al, 2013)

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Prior to eculizumab, there have been no approved drug therapies, and otherwise very limited supportive care options for patients with aHUS. Supportive care options used in clinical practice do not address the underlying complement dysregulation, and therefore do not substantially reduce complement-mediated TMA or reverse kidney dysfunction; nor do they eliminate the need for dialysis.

Plasma Exchange/Plasma Infusion

The lack of positive evidence is highlighted by the fact that despite the use of PE/PI, 33% to 40% of patients have been shown to either die or require dialysis following their first presentation with aHUS.(Caprioli et al. 2006; Noris et al. 2010; Sellier-Leclerc et al. 2007) At one year from diagnosis, 65% of all patients were shown to have died, to require dialysis, or to have permanent renal damage.(Caprioli et al, 2006) An analysis of 116 aHUS patients from the HUSnet Registry reported that patients treated with PE/PI showed comparably poor outcomes at one year compared with patients not treated with PE/PI as measured by the incidence of

hypertension, impaired kidney function, and neurological sequelae.(Riedl et al, 2011) Further, a multinational group of aHUS investigators recently concluded, “The data highlight the inadequate efficacy of management with plasma exchange or infusion and confirm the clinically relevant treatment effect of eculizumab on thrombotic microangiopathy and organ outcomes.”(Legendre et al, 2013)

PE/PI does not address the uncontrolled complement activation in aHUS patients. Studies demonstrate that platelet activation and TMA persist during PE/PI in aHUS patients, indicating that PE/PI does not target the underlying disease process.(Stahl et al, 2008; Licht et al, 2009). In the eculizumab international clinical trials, patients continued to demonstrate TMA prior to eculizumab despite being on PE as measured by on-going platelet consumption.

In addition to the lack of efficacy of PE/PI, the procedure is also associated with significant safety concerns. In a cohort of 249 adult TMA patients treated with plasma exchange, 26% of patients experienced major complications including:

- death in 3% of patients,
- systemic infection in 12% of patients,
- non-fatal cardiac arrest in 1% of patients,
- hypotension requiring vasopressor treatment in 3% of patients, and
- thrombosis in 2% of patients.(George, 2010)

The rate of significant safety concerns is also strikingly high in children receiving apheresis.(Michon et al, 2007) Adverse events experienced by children included hypotension requiring fluid resuscitation (48%), hypocalcaemia (64%), severe anaemia (48%), and allergic reactions (24%). Additional safety concerns due to venous access have been reported in children receiving apheresis, including catheter-related infections (16%), catheter-related thrombosis (12%), and central venous obstruction (20%).(Michon et al, 2007)

Prior to the availability of eculizumab, two advisory groups provided guidance for clinicians on the use of PE/PI in aHUS. Documents published in 2009 provide non-evidence-based recommendations on use of PE/PI as the initial supportive care option for aHUS patients. Importantly, however, the authors of one guideline consider the strength of their recommendation as “weak” and the quality of evidence supporting the recommendation as “low”.(Taylor et al, 2010) Meanwhile, the authors of the second guideline state that: “This guideline for the investigation and initial treatment of atypical haemolytic uraemic syndrome [using PE/PI] is intended to offer an approach based on opinion, as evidence is lacking”.(Ariceta et al, 2009)

Dialysis

Dialysis (both peritoneal and haemodialysis) is a standard supportive measure for patients with acute or irreversible kidney damage. However, in aHUS, dialysis has no impact on the underlying complement dysregulation and consequently, on-going evidence of TMA is observed in aHUS patients receiving dialysis.(Donne et al, 2002; Larakeb et al, 2007; Davin et al, 2010) One year survival after TMA on dialysis is poor at only 58%.(Perkins et al, 2006)

In addition, a significantly decreased survival rate has been reported generally in all patients undergoing dialysis. The overall five-year survival rate of dialysis patients in 2004 in the United States and Europe was only 35% to 39%, indicating generally poor long-term outcomes. (United States Renal Data System, 2011; European Renal

Association, 2011) Together, this evidence demonstrates that high mortality in dialysis patients is compound in aHUS by on-going complement-mediated TMA in patients receiving supportive care alone.

Kidney Transplantation

Kidney transplantation does not rectify the continued and uncontrolled complement activation leading to progressive disease and premature mortality in aHUS patients. Renal transplantation is rarely performed in these patients due to a 60% graft loss by one year which stems from chronic uncontrolled complement activation and the resulting on-going systemic TMA, making kidney transplantation generally contraindicated prior to the availability of eculizumab.(Noris et al, 2010) Combined liver-kidney transplantation is only available for very few patients, due to the limited supply of solid organs, and the substantial near-term risk of mortality which is deemed to be too high by many physicians and patients.(Loirat et al, 2008) Given the poor outcomes, isolated renal transplantation is often contraindicated in aHUS patients.(Zuber et al, 2011)

Published clinical data on the use of eculizumab in patients with aHUS have demonstrated significant clinical benefits. The authors concluded that eculizumab has the potential to become the standard of care in aHUS.(Licht et al 2011).

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

The pathway of care for patients with aHUS will be relatively unchanged save for the introduction of eculizumab as the primary targeted therapy once the diagnosis of aHUS has been established since supportive care such as PE/PI has no evidence of positive benefit in aHUS patients.

aHUS is a chronic and life-threatening disease. Eculizumab is indicated as a chronic therapy in all patients with a diagnosis of aHUS and in line with the licensed indication and clinical trials, eculizumab is recommended for the treatment of all patients with a clinical diagnosis of aHUS. Clinical diagnosis of aHUS is based on presence of the following signs and symptoms of complement-mediated TMA, for example:

- Decreased platelet count
- Evidence of microangiopathic haemolysis (e.g., raised LDH or presence of schistocytes)
- Evidence of organ impairment/damage [e.g., serum creatinine > Upper Limit of Normal (ULN)]

Where clinically suspected, aHUS can be differentiated from other TMA diseases. ADAMTS13 activity greater than 5% excludes severe ADAMTS13 deficiency (congenital or acquired TTP) as a cause of TMA. The absence of positive Shiga-Toxin producing enterohaemorrhagic *Escherichia coli* (STEC) test excludes STEC-HUS as the sole cause of TMA.

Importantly, positive identification of complement gene mutations or auto-antibodies present in aHUS patients is not needed for diagnosis or initiation of eculizumab. Genetic mutation cannot be identified in 30% to 50% of patients clinically diagnosed with aHUS and who still have an equally poor outlook to those with identifiable complement mutations.(Noris et al, 2010)

Further, genetic screening cannot determine resistance to eculizumab treatment. First, the prospective clinical trials demonstrate that all patients benefit from eculizumab treatment independent of an identified complement mutation. Second, identification of the newly discovered mutation in the gene encoding for DGKe presenting in aHUS patients less than one year of age does not exclude the use of eculizumab. Lemaire et al reported seven DGKe patients being treated with eculizumab with one patient showing signs of TMA during eculizumab treatment. The other six patients were managed successfully with eculizumab. The investigators speculate on the potential role for DGKe in accelerating endothelial damage through PKC, which can lead to uncontrolled chronic complement activation and unmask aHUS. Therefore, based on the current evidence of the benefit of eculizumab in aHUS patients, the acceleration of disease in DGKe and six patients with a DGKe mutation reportedly responding to eculizumab, it is too early to assume that these high risk aHUS patients would need to be discontinued from eculizumab treatment until further investigation has been made.

Third and more broadly, a single nucleotide polymorphism in the gene encoding C5 has been reported in 2% of the Japanese population. The polymorphism is restricted to the Japanese population. All PNH patients treated with eculizumab in the UK and Western Europe have responded to eculizumab as measured by decline in LDH. Therefore, based on the large number of PNH-treated patients responding well to eculizumab, the likelihood of C5 polymorphism in UK patients receiving eculizumab is extremely low.

Clinical trials data have shown that early intervention with eculizumab is associated with optimal patient outcomes; therefore, eculizumab is intended for immediate primary treatment following diagnosis of aHUS. Published recommendations have advised that eculizumab should be commenced within 24 hours of aHUS disease onset.(Zuber et al, 2012a) The SmPC recommends that eculizumab treatment be continued for the patient's lifetime. Severe TMA complications were observed in patients who discontinued therapy with eculizumab.(SmPC, 2013)

Presently, no approved drug therapies, and otherwise very limited supportive care options, exist for patients with aHUS. Currently available supportive care options that are utilised in the clinical care pathway are aimed at trying to stabilise haematological parameters, defined as normalisation of platelet count and reduction in haemolysis.(Loirat et al, 2008; Ariceta et al, 2009) These supportive care options do not address uncontrolled complement activation, do not substantially reduce complement-mediated TMA or reverse kidney dysfunction, nor do they eliminate the need for new dialysis or positively impact patient survival. Moreover, the available supportive care options likely contribute to a further debilitating quality of life for surviving aHUS patients.

It is recognised that an aHUS patient may present at any time and hospital location across England. It will therefore be important to ensure that any suspected diagnosis of aHUS be confirmed as soon as possible in order to try to prevent significant and life-long renal impairment or other irreversible organ damage. Such diagnosis could be supported by centre/s of expertise working a part of a "national aHUS service" whereby local centres would have immediate access to expert advice relating to diagnosis and early appropriate management of aHUS cases. Once diagnosis has been confirmed, management of the patient would continue within the local setting supported by on-going monitoring and evaluation provided in conjunction with the centre/s of expertise. Clearly, the establishment of a national aHUS service will be the remit of NHS England following a national commissioning direction.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

aHUS is a devastating, life-threatening, and ultra-rare disease in which excessive, chronic, uncontrolled complement activation in all patients causes a life-long risk for catastrophic outcomes: in the pre-eculizumab era, 65% of all patients have died, require dialysis, or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion.(Neuhaus et al, 1997; Caprioli et al, 2006; Noris et al, 2010)

Eculizumab is the first and only complement inhibitor available worldwide and the innovative nature of the drug has been recognised in both the US and France as a winner of the prestigious *Prix Galien* award for technology innovation. Eculizumab is also the first and only targeted therapy approved for the treatment of aHUS. Prior to regulatory approval of eculizumab for the treatment of aHUS in 2011, the only management options for this devastating disease were supportive in nature and therefore did not address the underlying cause of the condition. In contrast, eculizumab directly addresses the underlying cause of aHUS by inhibiting chronic, uncontrolled complement activation, thereby providing significant clinical benefit to patients with aHUS. As highlighted in recent peer-reviewed publications, notably the New England Journal of Medicine (Legendre et al 2013) and in various case study reports and case series, eculizumab alters immediate and long-term outcomes for patients with aHUS including inhibition of complement-mediated TMA, a significant time-dependent and continuous improvement in renal function, opportunity for cessation of dialysis, ability to prevent patients progressing to dialysis, improvement in extra-renal consequences, and significant improvement in patient reported quality of life. As such, eculizumab is a major technological and innovative breakthrough in the treatment of patients with a life-threatening, chronic, and ultra-rare disease.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Infrastructure requirements are limited to the additional resource requirements within the current centres of adult and paediatric expertise in Newcastle. No additional infrastructure will be required in local centres where aHUS patients may present.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Basic haematological parameters (haemoglobin, platelet count, lactate dehydrogenase, renal function (creatinine)) support the clinical diagnosis of aHUS. In patients where other causes of TMA are suspected, ADAMTS13 activity and shiga-toxin testing support the differentiation of TMAs and diagnosis of aHUS. Genetic testing and complement levels are not required for diagnosis of aHUS or eculizumab initiation. Patients should be monitored for TMA on a regular basis. These investigations are not particular to eculizumab use and are undertaken in all aHUS patients.

- TTP is caused by severe ADAMTS13 deficiency (<5% activity). Confirmation of activity > 5% supports the diagnosis of aHUS if TTP is clinically considered as a possible diagnosis.(Tsai, 2010; Tsai, 2013a)
- Testing for Shiga-toxin can help identify STEC-HUS patients, but these patients should also be evaluated for aHUS as STEC can be a triggering factor for first presentation of aHUS.(Ariceta et al, 2009)
- Genetic testing is not required for aHUS diagnosis or eculizumab initiation: Up to 50% of aHUS patients do not have an identifiable genetic mutation.(SmPC, Noris et al 2010)

Eculizumab (Soliris) should only be administered via intravenous infusion. The diluted solution of Soliris should be administered by intravenous infusion over 25 to 45 minutes via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of Soliris from light during administration to the patient.

Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults and adolescents and four hours in children aged less than 12 years.(SmPC, 2013)

The blockade of terminal complement activation and the generation of C5b-9 increase the risk of meningococcal infection; therefore, use of eculizumab increases an unvaccinated patient's susceptibility to serious meningococcal infections (*Neisseria meningitides*). As indicated in the FDA-approved label and EMA SmPC, all patients must be vaccinated at least two weeks prior to receiving Soliris to reduce the risk of infection. Patients below the age of two years and those who are treated with eculizumab less than two weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, C, Y and W135 are strongly recommended, preferably conjugated ones.

Eculizumab should not be administered to patients with unresolved *Neisseria meningitides* infection or to patients who have not been vaccinated against *Neisseria meningitides* unless they are being treated with appropriate antibiotic prophylaxis.

It is recommended that patients being treated with eculizumab be monitored for early signs of meningococcal infection. Patients should carry a safety card with them at all times.

There were no meningococcal-related deaths in the aHUS clinical studies. There were three patients in the trial that had meningococcal infections; all three patients recovered and two patients continued in the trial. Furthermore, there did not appear to be evidence for an increased risk of other serious infections with eculizumab treatment in the aHUS studies. Adverse events reported to the aHUS clinical studies are described in more detail below. All patients on eculizumab should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with antibiotics if necessary.

Patients on eculizumab therapy should also be monitored routinely for TMA by measurement of platelet count, serum LDH, and serum creatinine.

Other than meningococcal vaccination and antibiotic prophylaxis mentioned above, no other therapies are required or recommended to be administered concomitantly with eculizumab.

In terms of administration itself, Alexion funds the aHUS homecare service, which will be available to all aHUS patients undergoing treatment with eculizumab in England.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Eculizumab is simple to administer via intravenous infusion and is generally well-tolerated. Therefore, it is suitable for administration at appropriate centres throughout England.

Due to the urgency of treatment, eculizumab will be initiated in local centres with the support of centre/s of expertise. It is envisaged that most patients will transition to home care, whereby on-going follow-up will be provided by centre/s of expertise as defined and agreed by NHS England.

Given that expertise in the field is very limited owing to the low number of aHUS patients presenting annually it is envisaged that centres of expertise will be drawn from existing renal unit/s across England. Currently, the management of aHUS and prescription of eculizumab is led by Professor Tim Goodship, an adult nephrologist with an international reputation in the field of aHUS. His research group was the first to identify that mutations in complement regulators led to the development of the disease and subsequently many of the landmark papers in the field have emanated from his laboratory. Professor Goodship currently devotes much of his time supporting physicians from around the UK (and outside of the UK) with diagnostic and management queries. The group in Newcastle, including Professor Neil Sheerin, who is an expert in renal transplantation and complement, and Dr David Kavanagh, who has recently been awarded a Wellcome Trust Intermediate Clinical Fellowship for a project titled “The convergence of complement and coagulation in atypical haemolytic uraemic syndrome’, provide a referral service for all renal and haematology centres in England for assessment and management of patients with a diagnosis aHUS, including recommendation regarding the use of eculizumab for both incident and prevalent cases.

The paediatric referral service is being led by Dr Sally Johnson, a paediatric nephrologist with considerable experience in the management of aHUS in children. Working with her adult colleagues in Newcastle, Dr Johnson provides support to all paediatric units in England regarding the assessment and management of patients with aHUS, including the use of eculizumab in both incident and prevalent cases.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is envisaged that with prompt and accurate diagnosis on first presentation of aHUS, use of Plasma exchange/plasma infusion will be reduced or eliminated. Subsequent dependence upon dialysis for support of patients in end stage renal disease as a result of aHUS will be reduced or eliminated.

Implementation of a ‘centre/s of expertise’ network and disease education programmes will improve speed of diagnosis and diagnostic accuracy thus alleviating the ‘diagnostic odyssey’ of patients. This will reduce the need for repeated investigations and tests and potential interventions which impact significantly on NHS resources and patient outcomes.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A comprehensive search was conducted to identify all studies on the clinical effectiveness of eculizumab. Three strategic approaches were used:

- A search of the published literature (EMBASE and MEDLINE);
- A search of registers of randomised trials; and
- Manual checking of reference lists of all relevant articles.

Before conducting the literature searches, entry criteria were defined for the inclusion and exclusion of papers. To be included, a reference had to report a clinical trial that met all the following criteria:

- A randomisation procedure in the trial design;
- Comparison of eculizumab versus supportive care, or alternatively was a placebo controlled eculizumab trial; and
- Participant characteristics consistent with atypical Haemolytic Uraemic Syndrome (aHUS).

The term 'atypical' was first used to describe non-diarrhoeal associated Haemolytic Uraemic Syndrome (HUS) as long ago as 1965. HUS is characterised by a combination of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. Since then, aHUS has been described as non-diarrhoeal HUS and non-shiga-toxin HUS (non- Shiga-Toxin producing enterohaemorrhagic *Escherichia coli* (STEC) HUS), but increasingly over the past decade, aHUS has become recognised as a disease process readily differentiated from HUS. For this reason, searching the literature for appropriate trials required a complex process. There are no reliable terms that apply to the majority of the literature on aHUS. Terminology that surrounds and sometimes refers to the disease that is aHUS includes: thrombotic microangiopathy (TMA), thrombotic thrombocytopaenic purpura (TTP), ADAMTS13, complement mutation, non-STEC-HUS and non-diarrhoeal HUS. This resulted in a relatively large number of publications (over 1,000), which needed to be assessed using either abstract or full text. Hand searching reference lists of important publications was necessary in order to identify relevant publications and to prevent overlap of study populations under different authors.

The following primary selection criteria were used:

- Children and adults with atypical haemolytic uraemic syndrome (aHUS); and
- Patients with typical or acquired haemolytic uraemic syndrome or without atypical haemolytic uraemic syndrome were excluded from the assessment.

Secondary journal level search criteria included the following requirements:

- The initial selection include human, English-language only; and
- The highest level of available evidence to be included.

Seven reviews were identified in the search. However, all were reviewed and none were relevant to the Final Scope as outlined by NICE. Two results for 'aHUS' were incomplete at the time of the search (one project record and another structured abstract), and the remaining five were not relevant to aHUS treatment.

Details of the search strategies used to identify relevant studies for the indirect comparison are presented in Appendix 17.1 along with search results annotated with the reasons for inclusion or exclusion of trials.

Full citation details and abstracts of all studies identified in the searches were downloaded and reviewed. If a paper could not be excluded on the basis of the information in the title or abstract, the full paper was retrieved before any decision was made. Duplicate citations were removed and all relevant papers retrieved.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Unpublished studies were identified from Alexion-sponsored clinical trials as well as clinical trial registries. Only Alexion-sponsored trials were included in the assessment as having sufficient data available for assessment.

9.2 Study selection

Published studies

9.2.1 Complete Table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1: Selection criteria used for published studies

Search location	Search strategy (eculizumab focus)	Citations retrieved	Total citations for RCTs	Total citations for non-RCTs
Medline 19 June 2013 (human, English language)	#1: atypical haemolytic uremic syndrome or atypical HUS or aHUS or non-diarrheal HUS or non Stx HUS (mp)	394		
	# 2: complement and allotransplantation	27		

Search location	Search strategy (eculizumab focus)	Citations retrieved	Total citations for RCTs	Total citations for non-RCTs
	#3: Complement C5	320		
	#4: haemolysis and complement	416		
	#5: eculizumab	264		
	# 6: randomized controlled trial.mp. OR Randomized Controlled Trial	197217		
	#7: #1 OR #2 OR #3 OR #4 OR #5	1221		1013
	#8: #6 AND #7	25	25	0
Embase 4 July 2013	#1: atypical haemolytic uremic syndrome or atypical HUS or aHUS or non-diarrheal HUS or non Stx HUS (mp)	594		
	# 2: complement and allotransplantation (mp)	126		
	#3: Complement C5 (mp)	103		
	#4: haemolysis and complement	986		
	#5: eculizumab	1127		
	#6: randomized controlled trial.mp. OR Randomized Controlled Trial	250408		
	#7: #1 OR #2 OR #3 OR #4 OR #5	2609		2552
	#8: #7 AND #6 (limited to RCTs)	57	57	0
Cochrane Library Review & CCTR	#1: Eculizumab	9	4	5
	#2: Atypical haemolytic-uremic syndrome	2	0	2
Clinicaltrials.gov	#1: Eculizumab AND Atypical haemolytic-uremic syndrome	6	0	6
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]				

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

9.2.2.1. Published RCT studies included and exclude at each stage of search

The below PRISMA flow diagram (Figure C1) and summary table (Table C2) describe the number of published RCT studies identified then included or excluded in the analysis.

Figure C1: PRISMA diagram, included and excluded RCT studies

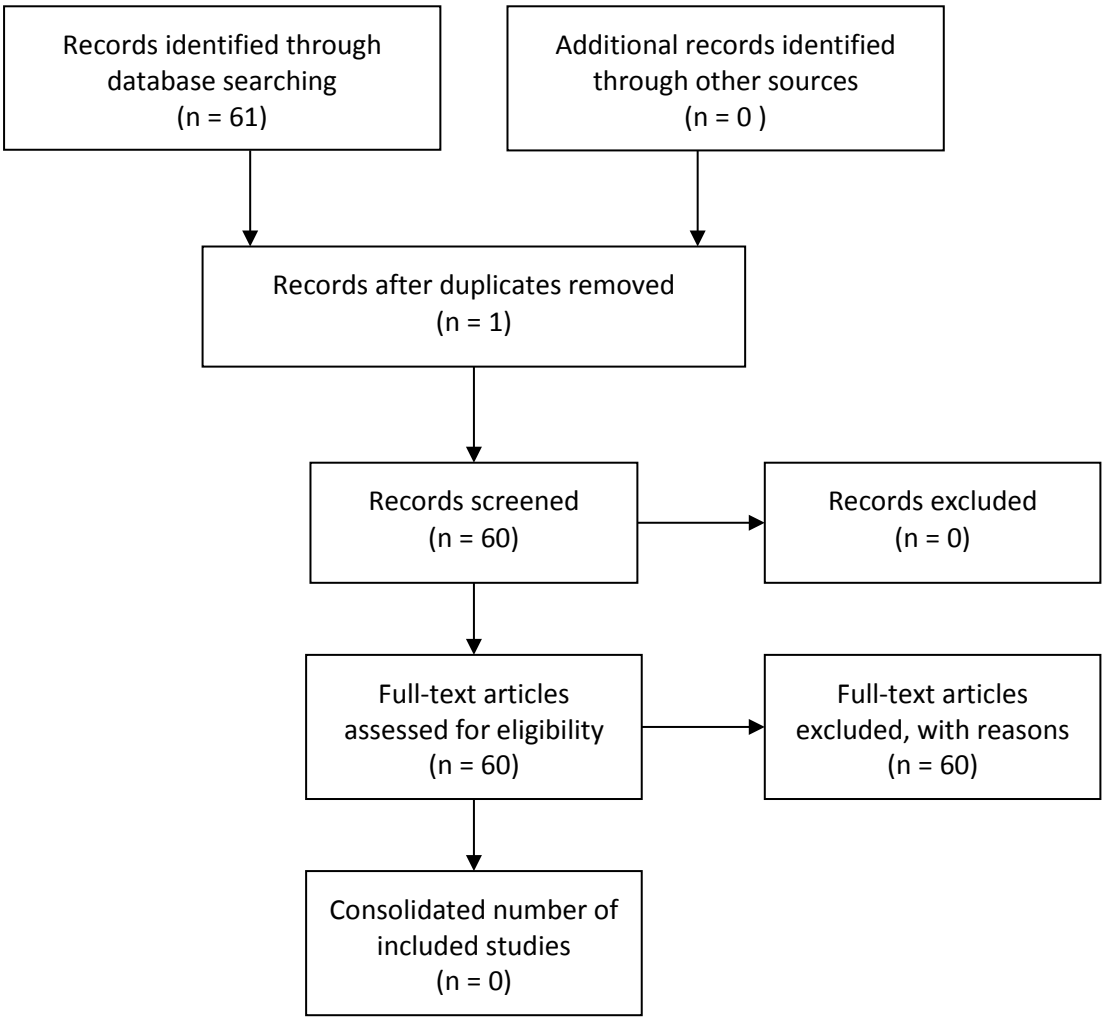


Table C2: Summary of search output exclusions (RCT Search)

	Citations retrieved		
Eculizumab Search	**EMBASE including Medline**	**Cochrane CCTR**	**NIH**
Number of citations retrieved by search	57	4	0
Identical Duplicate	1		
Number Reviewed	56	4	0
Number of citations excluded after title/abstract review: A: not a randomised trial	21		
B: randomised trial does not include the proposed drug and the main comparator in separate arms	1		
C: characteristics of the recruited participants do not overlap with the main indication	34	4	
Consolidated number of citations of direct randomized trials	0	0	0
Number of multiple (additional) citations of direct randomised trials identified	0	0	0
Number of citations of direct randomized trials	0	0	0

9.2.2.2. Published non-RCT studies included and exclude at each stage of search

Due to the lack of high level evidence in the form of randomised controlled trials, the term ‘trial’ was extended to include case series, retrospective trials, registries, cohort and case studies. The below PRISMA flow diagram (Figure C2) and summary table (Table C3) describe the number of published non-RCT studies identified then included or excluded in the analysis.

Figure C2: PRISMA diagram, included and excluded non-RCT studies

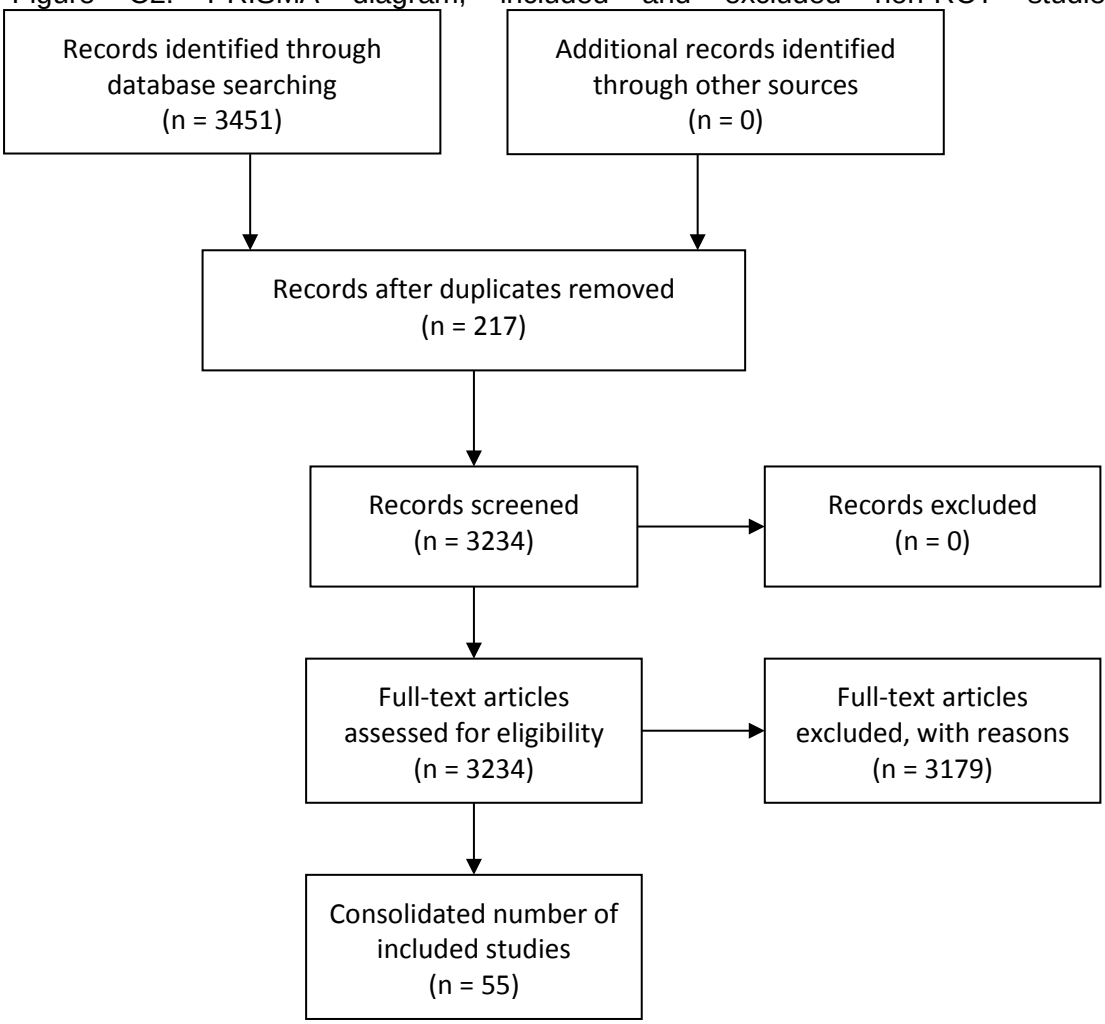


Table C3: Summary of search output exclusions (Non-Randomised Trials Search)

	Citations retrieved		
Search	**EMBASE including Medline**	**Cochrane CCTR**	**NIH**
Number of citations retrieved by search	3425	7	19
Identical Duplicates	217	0	0
Number Reviewed	3208	7	19
Number of citations excluded after title/abstract review: A: Did not include eculizumab or comparative interventions B: characteristics of the recruited participants do not overlap with the main indication C: Not a trial but other type of papers, e.g. commentary D: Studies were *in-vitro*	3153	7	19
Consolidated number of citations of included studies	55	0	0
Number of multiple (additional) citations of trials identified	0	0	0
Number of citations of studies	55	0	0

Unpublished studies

9.2.3 Complete the table below to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Unpublished studies were identified from the above described search strategy (see Table C1), including search of clinical trial registries and sponsored clinical development program. The relevant studies included two prospective, single-arm, controlled trials in paediatric and adult patients with aHUS (C10-003 and C10-004, respectively). One observational long-term extension study (C11-003) and one observational registry study (M11-001) were also identified.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

No unpublished studies relevant to the scope as described above were excluded.

*9.3 **Complete list of relevant studies***

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tablesTable C1.

No studies were identified that compare the intervention with relevant comparators. The list of published and unpublished studies includes four prospective, controlled, single-arm studies (registration trials C08-002 and C08-003, and additional prospective trials C10-003 and C10-004). The first two trials have been published as a full manuscript (Legendre et al, 2013) as well as multiple abstracts. The latter two trials are presented as unpublished interim data analysis. Two additional observational studies (C11-003, long-term extension of prospective trials and M11-001, international aHUS registry) are also included.

As described in Section 9.2.2.2, the term 'trial' was extended to include case series, retrospective trials, registries, cohort and case studies due to the lack of high level evidence in the form of randomised controlled trials. The search identified 60 case reports and 2 case series describing the use of eculizumab in patients with aHUS (Table C4, Table C5).

Table C4: List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Alexion-sponsored trials				
Al-Akash 2012	C09-001r	Adult, adolescent, and paediatric patients with clinical diagnosis of aHUS	Eculizumab	n/a
Legendre 2013, Trial 1	C08-002A/B	Adult and adolescent patients with clinical diagnosis of aHUS and progressing TMA	Eculizumab	n/a
Legendre 2013, Trial 2	C08-003A/B	Adult and adolescent patients with clinical diagnosis of aHUS and long duration of disease	Eculizumab	n/a
Case reports and case series				
Alachkar 2012		Case report	Eculizumab	n/a
Al-Akash 2011		Case report	Eculizumab	n/a
Alberti 2013		Case series	Eculizumab	n/a
Ariceta 2012		Case report	Eculizumab	n/a
Besbas 2013		Case report	Eculizumab	n/a
Brown 2012		Case report	Eculizumab	n/a
Carr 2013		Case report	Eculizumab	n/a
Cayci 2012		Case report	Eculizumab	n/a
Chao 2012		Case report	Eculizumab	n/a
Chatelet 2010		Case report	Eculizumab	n/a
David 2013		Case report	Eculizumab	n/a
Davin 2009		Case report	Eculizumab	n/a
Davin 2010		Case report	Eculizumab	n/a
De 2010		Case report	Eculizumab	n/a
De Latour 2013		Case report	Eculizumab	n/a
Delmas 2013		Case report	Eculizumab	n/a
Dorresteijn 2012		Case report	Eculizumab	n/a
Durán 2012		Case report	Eculizumab	n/a
Garjau 2012		Case report	Eculizumab	n/a
Giordano 2012		Case report	Eculizumab	n/a
Gnappi 2012		Case report	Eculizumab	n/a

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Gruppo 2009		Case report	Eculizumab	n/a
Gulleroglu 2013		Case report	Eculizumab	n/a
Gupta 2011		Case report	Eculizumab	n/a
Heinen 2013		Case report	Eculizumab	n/a
Hepgur 2012		Case report	Eculizumab	n/a
Hodgkins 2012		Case report	Eculizumab	n/a
Kalmanovich 2012		Case report	Eculizumab	n/a
Kim 2012		Case report	Eculizumab	n/a
Kose		Case report	Eculizumab	n/a
Kourouklaris 2013		Case report	Eculizumab	n/a
Krid 2012		Case report	Eculizumab	n/a
Lapeyraque 2011		Case report	Eculizumab	n/a
Larrea 2011		Case report	Eculizumab	n/a
Loirat 2010		Case report	Eculizumab	n/a
Mache 2009		Case report	Eculizumab	n/a
Malina 2012		Case report	Eculizumab	n/a
Nester 2011		Case report	Eculizumab	n/a
Nürnberger 2009		Case report	Eculizumab	n/a
Ohanian 2011a		Case report	Eculizumab	n/a
Ohanian 2011b		Case report	Eculizumab	n/a
Pabst 2013		Case report	Eculizumab	n/a
Pelicano 2013		Case report	Eculizumab	n/a
Povey 2013		Case report	Eculizumab	n/a
Prescott 2010		Case report	Eculizumab	n/a
Salem 2013		Case report	Eculizumab	n/a
Sallee 2010		Case report	Eculizumab	n/a
Sethy 2012		Case report	Eculizumab	n/a
Totina 2013		Case report	Eculizumab	n/a
Totina 2011		Case report	Eculizumab	n/a
Tsai 2013		Case report	Eculizumab	n/a
Tschumi 2011		Case report	Eculizumab	n/a
Uslu-Gokceoglu 2013		Case report	Eculizumab	n/a
Vilalta 2012		Case report	Eculizumab	n/a
Weitz 2011		Case report	Eculizumab	n/a
Xie 2012		Case report	Eculizumab	n/a
Yasuda 2013		Case report	Eculizumab	n/a

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Zimmerhackl 2010		Case report	Eculizumab	n/a
Zlamy 2012		Case report	Eculizumab	n/a
Zschiedrich 2013		Case report	Eculizumab	n/a
Zuber 2012a		Case series	Eculizumab	n/a
Zuber 2012b		Case series	Eculizumab	n/a

Table C5: List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Interim Clinical Study Report	C10-003	Paediatric aHUS patients	Eculizumab	n/a
Interim Clinical Study report	C10-004	Adult aHUS patients	Eculizumab	n/a
Clinical study protocol; analysis not yet available	C11-003	Paediatric and adult aHUS patients	Observational	n/a
Clinical study protocol; analysis not yet available	M11-001	aHUS patients	Observational	Observational

9.3.2 State the rationale behind excluding any of the published studies listed in tables Table C4 and Table C5.

All published and unpublished clinical trials that are relevant to the scope of the application have been included. Individual published case studies and case series have been excluded as level of relevant data is not available or they fall outside the scope of this submission due to population or dosing variability.

*9.4 **Summary of methodology of relevant studies***

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables Table C6 and Table C7 as appropriate. A separate table should be completed for each study.

Table C6 includes methodology of four controlled, prospective, open-label, Phase II, multi-centre clinical trials (C08-002, C08-003, C10-003, and C10-004).

Table C6 Summary of methodology for controlled trials

Study name	**Legendre 2013 Trial 1** (C08-002 A/B)
Objectives	Objectives: The following trial objectives for adolescent patients (from 12 and up to 18 years of age) with aHUS that have evidence of progressive TMA after four or more sessions of plasma exchange or infusion in the prior week are to: Primary: − Assess the effect of eculizumab to reduce TMA as indicated by thrombocytopenia as measured by platelet

Study name	**Legendre 2013 Trial 1** (C08-002 A/B)
	count change from baseline through the treatment period Secondary: − Evaluate additional efficacy endpoints such as the effect of eculizumab on: – TMA Intervention Rate (# Plasma exchange/ Plasma infusion (PE/PI) and # Dialysis Events/Patient/Day) during the Treatment Period compared with the TMA Intervention Rate prior to the first dose – TMA-Event Free status defined as the absence of [1] decrease in platelet count of > 25% from the Platelet Count Pre-PT Baseline Set-Point; [2] PE/PI while the patient is receiving eculizumab, and [3] new dialysis for at least 12 weeks. – Key Haemolytic measures. – Quality of Life measures. – Renal function measures. – TMA Remission. • Characterise the overall safety and tolerability of eculizumab. • Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in patients with aHUS. • Perform a series of exploratory efficacy analyses such as the effect of eculizumab on: − Platelet count measures. − Thrombotic measures. − Pro-inflammatory markers. − Major Adverse Vascular Events (MAVE). − Systemic hypertension and anti-hypertensive medication. − Additional haemolytic measures. − Additional measures of renal function.
Location	30 centres in North America (Canada, US) and Europe (Austria, France, Germany, Italy, Netherlands, Spain, Sweden, UK)
Design	Open-label, non-randomised, single-arm multi-centre controlled trial including the following study periods: 1. Screening (max 3 days) 2. Treatment (26 weeks) 3. Follow-up if eculizumab was discontinued (8 weeks)
Duration of study	26 weeks; patients allowed to continue in long-term extension until product registered and available
Sample size	17 (16 adults, 1 adolescent)
Inclusion criteria	• Male/female; age ≥12 years • Weight ≥ 40kg • Clinical diagnosis aHUS (newly diagnosed, existing diagnosis, or post-transplant) • LDH > Upper Limit of Normal (ULN) • PE/PI: ≥ 4 sessions in the week prior to screening

Study name	**Legendre 2013 Trial 1** (C08-002 A/B)
	• Platelet count <150 x 10^9/L and at least 25% lower than average of 3 platelet counts obtained during most recent TMA admission at least 1 month apart prior to screening • Serum creatinine ≥ ULN for age (acute dialysis for acute renal failure eligible; chronic dialysis not permitted) • No requirement for an identified complement mutation
Exclusion criteria	• Acquired or congenital TTP (ADAMTS13) deficiency, <5% activity) • History of malignancy within 5 years of screening • Typical HUS (shiga toxin positive) • Known HIV infection • Identified drug-exposure-related HUS • HUS-related bone marrow transplant • Confirmed sepsis (positive blood cultures within 7 days of screening and not treated with organism-sensitive antibiotic) • Active, untreated systemic bacterial infection that confounds diagnosis of aHUS or affects ability to manage aHUS • Pregnancy or lactation • Unresolved meningococcal disease • Known systemic lupus erythematous (SLE) • Previous treatment with eculizumab • Treatment with IVIG within 8 weeks or rituximab within 12 weeks of screening • Treatment with other immunosuppressive therapies • Treatment with erythrocyte-stimulating agents unless already on a stable dose for 4 weeks prior to screening.
Method of randomisation	N/A (non-randomised)
Method of blinding	N/A (single-arm)
Intervention(s) (n =) and comparator(s) (n =)	N/A (single-arm)
Baseline differences	N/A (single-arm)
Duration of follow-up, lost to follow-up information	8 weeks, if discontinued
Statistical tests	All primary analyses were performed in the intention-to-treat population. Means [±Standard Error (SE)], medians and ranges, least-squares means, and 95% confidence intervals were determined for all continuous variables. All 26-week results presented from models based on only the first 26 weeks of data
Primary outcomes (including scoring methods and timings of assessments)	• Reduction in TMA as measured by change in platelet count from baseline – Baseline set-point calculated as the average of two platelet counts collected immediately prior to the qualifying PE/PI – Platelet counts collected at each weekly visit thereafter

Study name	**Legendre 2013 Trial 1** (C08-002 A/B)
Secondary outcomes (including scoring methods and timings of assessments)	• Reduction in TMA as measured by TMA event-free status (defined as no decrease in platelet count of > 25% AND no PE/PI AND no new dialysis for ≥12 consecutive weeks) • TMA intervention rate (defined as the number of PE/PI interventions and the number of dialysis events per patient per day) • Improvement in or preservation of renal function: – Improvement in kidney function eGFR; CKD stage) – Reduction in ongoing kidney damage (Proteinuria) • Reduction in Burden of Disease • Improvement in Anemia • Improvement in Quality of life

Study name	**Legendre 2013 Trial 2** (C08-003A/B)
Objectives	Objectives: The following trial objectives for adult and adolescent (from 12 and up to 18 years of age) patients with plasma therapy-sensitive aHUS are to: Primary: • Assess the effect of eculizumab on TMA-Event Free status defined as the absence of [1] decrease in platelet count of > 25% from the Platelet Count Pre-PT Baseline Set-Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis for at least 12 weeks in adult and adolescent patients with aHUS with long duration of disease and renal impairment. Secondary: • Evaluate additional efficacy endpoints such as the effect of eculizumab on: − TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) during the Treatment Period compared with the TMA Intervention Rate prior to the first dose of eculizumab. − Reduction of TMA as indicated by thrombocytopenia as measured by platelet count change from baseline through the treatment period. − Key Haemolytic measures. − Quality of Life measures. − Renal function measures. − TMA Remission. • Characterise the overall safety and tolerability of eculizumab. • Describe the PK and PD of eculizumab in patients with aHUS. − Perform a series of exploratory efficacy analyses such as the effect of eculizumab on: − Platelet count measures. − Thrombotic measures. − Pro-inflammatory markers. − Major Adverse Vascular Event (MAVE).

Study name	**Legendre 2013 Trial 2** (C08-003A/B)
	− Systemic hypertension and anti-hypertensive medication. − Additional haemolytic measures. − Additional measures of renal function.
Location	30 centres in North America (Canada, US) and Europe (Austria, France, Germany, Italy, Netherlands, Spain, Sweden, UK)
Design	Open-label, non-randomised, single-arm multi-centre controlled trial including the following study periods: 1. Screening (max 2 days) 2. Treatment (26 weeks) 3. Follow-up if eculizumab was discontinued (8 weeks)
Duration of study	26 weeks; patients allowed to continue in long-term extension until product registered and available
Sample size	20 (15 adults, 5 adolescent)
Inclusion criteria	• Male/female; age ≥ 12 years • Weight ≥ 40kg • Clinical diagnosis aHUS (newly diagnosed, existing diagnosis, or post-transplant) • LDH and creatinine > ULN • PE/PI: ≥1 session / 2 weeks and ≤3 sessions/week for ≥8 w eeks before first dose of eculizumab • No platelet decrease > 25% during 8 weeks prior to first dose of eculizumab • Serum creatinine ≥ ULN for age (chronic dialysis permitted) • No requirement for an identified complement mutation
Exclusion criteria	• Acquired or congenital TTP (Severe ADAMTS13 deficiency, <5% activity) • History of malignancy within 5 years of screening • Typical HUS (shiga toxin positive) • Known HIV infection • Identified drug-exposure-related HUS • HUS-related bone marrow transplant • Confirmed sepsis (positive blood cultures within 7 days of screening and not treated with organism-sensitive antibiotic) • Active, untreated systemic bacterial infection that confounds diagnosis of aHUS or affects ability to manage aHUS • Pregnancy or lactation • Unresolved meningococcal disease • Known systemic lupus erythematous (SLE) • Previous treatment with eculizumab • Treatment with IVIG within 8 weeks or rituximab within 12 weeks of screening • Treatment with other immunosuppressive therapies • Treatment with erythrocyte-stimulating agents unless already on a stable dose for 4 weeks prior to screening.

Study name	**Legendre 2013 Trial 2** (C08-003A/B)
Method of randomisation	N/A (non-randomised)
Method of blinding	N/A (single-arm)
Intervention(s) (n =) and comparator(s) (n =)	N/A (single-arm)
Baseline differences	N/A (single-arm)
Duration of follow-up, lost to follow-up information	8 weeks, if discontinued
Statistical tests	All primary analyses were performed in the intention-to-treat population. Means (±SE), medians and ranges, least-squares means, and 95% confidence intervals were determined for all continuous variables. All 26-week results presented from models based on only the first 26 weeks of data
Primary outcomes (including scoring methods and timings of assessments)	• Reduction in TMA as measured by TMA event–free status (defined as no decrease in platelet count of > 25% AND no PE/PI AND no new dialysis for ≥12 consecutive weeks)
Secondary outcomes (including scoring methods and timings of assessments)	• Reduction in TMA as measured by change in platelet count from baseline − Baseline set-point calculated as the average of two platelet counts collected immediately prior to the qualifying PE/PI − Platelet counts collected at each weekly visit thereafter • TMA intervention rate (defined as the number of PE/PI interventions and the number of dialysis events per patient per day) • Improvement in or preservation of renal function: − Improvement in kidney function (eGFR; CKD stage) − Reduction in ongoing kidney damage (Proteinuria) • Reduction in Burden of Disease • Improvement in Anemia • Improvement in Quality of life

Study name	**C10-003**, "An open-label multi-centre clinical trial of eculizumab in paediatric patients with aHUS" (Unpublished)
Objectives	Assess the safety and efficacy of eculizumab in paediatric patients to control TMA as characterised by thrombocytopenia, haemolysis, and renal impairment
Location	[redacted]
Design	Controlled, single-arm, open-label
Duration of study	26 weeks
Sample size	22
Inclusion criteria	• Paediatric patients diagnosed with aHUS • Age 1 month to 18 years, ≥ 5 kg • Platelet count < Lower Limits of Normal (LLN) at screening and baseline • Evidence of haemolysis (LDH ≥ 1.5 x ULN and haemoglobin < LLN) at start of current aHUS event • Serum creatinine ≥ 97 percentile for age at screening

Study name	**C10-003**, "An open-label multi-centre clinical trial of eculizumab in paediatric patients with aHUS" (Unpublished)
	• Vaccinated against *N. meningitides*, pneumococcus and haemopholis at least 14 days prior to study or protected by prophylactic antibiotics • No requirement for identified complement mutation or antibody
Exclusion criteria	• ADAMTS13 activity < 5% • Positive shiga toxin test • > 5 weeks PE/PI prior to enrolment
Method of randomisation	Non-randomised
Method of blinding	Open-label
Intervention(s) (n =) and comparator(s) (n =)	Eculizumab (n=22)
Baseline differences	n/a
Duration of follow-up, lost to follow-up information	[redacted]
Statistical tests	[redacted] [redacted]
Primary outcomes (including scoring methods and timings of assessments)	• Complete TMA response confirmed by two consecutive measurements obtained at least four weeks apart − Haematologic normalisation (platelet count and LDH) − ≥ 25% improvement in serum creatinine from baseline
Secondary outcomes (including scoring methods and timings of assessments)	• Complete haematologic response (platelet count and LDH) sustained by two consecutive measurements obtained at least four weeks apart • Platelet count improvement: − Platelet count ≥ 150 x 10^9/L − Platelet count change from baseline • Renal function measures: − CKD stage − Decrease of serum creatinine [redacted] • New dialysis event-free status • Change in quality of life measures (Paediatric Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) fatigue) • Safety and tolerability • [redacted]

Study name	**C10-004**, "An open-label multi-centre clinical trial of eculizumab in adult patients with aHUS" (Unpublished)

Study name	**C10-004**, "An open-label multi-centre clinical trial of eculizumab in adult patients with aHUS" (Unpublished)
Objectives	Assess the safety and efficacy of eculizumab in paediatric patients to control TMA as characterised by thrombocytopenia, haemolysis, and renal impairment
Location	[redacted]
Design	Controlled, single-arm, open-label
Duration of study	26 weeks
Sample size	41
Inclusion criteria	• Adult patients (age ≥ 18 years) diagnosed with aHUS • Platelet count < LLN at screening and baseline • Evidence of haemolysis (LDH ≥ 1.5 x ULN and haemoglobin < LLN) at start of current aHUS event • Serum creatinine ≥ 97 percentile for age at screening • Vaccinated against *N. meningitides*, pneumococcus and haemopholis at least 14 days prior to study or protected by prophylactic antibiotics • No requirement for identified complement mutation or antibody
Exclusion criteria	• ADAMTS13 activity < 5% • Positive shiga toxin test
Method of randomisation	Non-randomised
Method of blinding	Open-label
Intervention(s) (n =) and comparator(s) (n =)	Eculizumab (n=41)
Baseline differences	[redacted]
Duration of follow-up, lost to follow-up information	[redacted]
Statistical tests	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	• Complete TMA response confirmed by two consecutive measurements obtained at least four weeks apart − Haematologic normalisation (platelet count and LDH) − < 25% worsening in serum creatinine from baseline
Secondary outcomes (including scoring methods and timings of assessments)	• Complete haematologic response (platelet count and LDH) sustained by two consecutive measurements obtained at least four weeks apart • Platelet count improvement: − Platelet count ≥ 150 x 10^9/L − Platelet count change from baseline • Renal function measures: [redacted]

Study name	**C10-004**, "An open-label multi-centre clinical trial of eculizumab in adult patients with aHUS" (Unpublished)
	− Decrease of serum creatinine [redacted] • New dialysis event-free status • Change in quality of life measures (Paediatric FACIT-F fatigue) • Safety and tolerability • [redacted]

Table C7 describe methodology of three retrospective and/or observational studies (C09-001r, C11-003, and M11-001).

Table C7: Summary of methodology for observational studies

Study name	**C09-001r**, A retrospective, observational, non-interventional trial to assess eculizumab treatment effect in patients with aHUS (Unpublished)
Objective	To assess safety and efficacy of eculizumab in aHUS patients treated outside of Alexion-sponsored controlled clinical trials
Location	Multi-national
Design	Retrospective, observational, non-interventional chart review
Duration of study	Variable
Patient population	Paediatric and adult patients with aHUS
Sample size	30
Inclusion criteria	• Male or female patients of any age who had been diagnosed with aHUS. • Received at least one dose of eculizumab for the treatment of aHUS between 2007 and Dec 2009 outside of an Alexion-sponsored controlled clinical trial.
Exclusion criteria	• Patients who had participated or who were concurrently participating in a controlled clinical trial of eculizumab
Intervention(s) (n =) and comparator(s) (n =)	Eculizumab (n=30); variable dosing schedule and treatment duration
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	n/a
Statistical tests	[redacted]

Study name	**C09-001r**, A retrospective, observational, non-interventional trial to assess eculizumab treatment effect in patients with aHUS (Unpublished)
	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	• Platelet count change from baseline and platelet count normalisation • Difference in TMA Intervention Rates (Pre- and During Treatment) • TMA Event-Free status
Secondary outcomes (including scoring methods and timings of assessments)	• Changes in Haemoglobin • Changes in LDH • Renal Function • Intravascular Haemolysis [redacted]

Study name	**C11-003**, aHUS Observational Long Term Follow-up (Unpublished)
Objective	Assess the long term safety and efficacy of eculizumab in patients with aHUS who have previously participated in an eculizumab study
Location	Multinational
Design	Phase IV observational, long term follow-up
Duration of study	[redacted]
Patient population	[redacted]
Sample size	Data not yet available
Inclusion criteria	aHUS patients who participated in any aHUS-eculizumab clinical studies
Exclusion criteria	
Intervention(s) (n =) and comparator(s) (n =)	Eculizumab (n=data not yet available)
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	[redacted]
Statistical tests	[redacted]

Study name	**C11-003**, aHUS Observational Long Term Follow-up (Unpublished)
	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	[redacted]TMA complication-free survival [redacted]
Secondary outcomes (including scoring methods and timings of assessments)	• Duration of response [redacted] • Change in value over time [redacted] – Platelet count – LDH – eGFR – serum haemoglobin – TMA intervention rate

Study name	**M11-001**, aHUS registry (Unpublished)
Objective	To capture post-marketing safety data on patients treated with eculizumab and collect information on the progression of disease in all aHUS patients receiving eculizumab or other disease management
Location	Multinational
Design	Observational, non-interventional
Duration of study	[redacted]
Patient population	Data not yet available
Sample size	Data not yet available
Inclusion criteria	Any patient with a diagnosis of aHUS, including: – Clinical diagnosis of aHUS – Patients with or without identified complement regulatory factor genetic abnormality or anti-complement factor antibody – ADAMTS13 > 5% (if performed)
Exclusion criteria	HUS only due to shiga toxin
Intervention(s) (n =) and comparator(s) (n =)	Eculizumab = Data not available
Baseline differences	Data not available

Study name	**M11-001**, aHUS registry (Unpublished)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Data collected at study enrolment and every six months thereafter.
Statistical tests	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	The proportion of patients who experience and the time to first and subsequent occurrence of the following events: [redacted] – death, – [redacted], – TMA complications of aHUS
Secondary outcomes (including scoring methods and timings of assessments)	[redacted]

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

The main registration trials for eculizumab in aHUS included two phase II prospective, controlled single-arm trials (C08-002A/B and C08-003A/B) and a retrospective chart review (09-001r). Overlapping data from these trials have been

analysed in clinical study reports, published in multiple abstracts, and in a full manuscript as follows:

C08-002A/B:

- Clinical study report: An open-label, multi-centre controlled clinical trial of eculizumab in adult/adolescent patients with plasma therapy-resistant atypical haemolytic-uremic syndrome (aHUS)

- Meeting abstracts:

    - Legendre et al 2010. Safety & Efficacy of Eculizumab in aHUS Patients Resistant to Plasma Therapy: Interim Analysis from a Phase II Trial. American Society of Nephrology, abstract SA-FC406.

    - Greenbaum et al 2011. Continued Improvements in Renal Function with Sustained Eculizumab in Patients aHUS Resistant PE/PI; American Society of Nephrology, abstract TH-PO367.

    - Legendre et al 2012. Eculizumab in aHUS Patients with Progressing TMA: Continued Improvements at 2-year Follow-Up; American Society of Nephrology, abstract SA-OR101

    - Greenbaum et al 2012. Eculizumab in aHUS patients with Progressing TMA: 2-year Data. American Society of Hematology, abstract 2084.

    - Goodship et al 2012. Eculizumab is effective in Patients with aHUS Regardless of Underlying Genetic Mutations or CFH Auto-antibodies. American Society of Nephrology, abstract TH-PO442.

    - Gaber et al 2013. Eculizumab Maintains Efficacy in aHUS Patients with Progressing TMA: 3-year Update. American Society of Nephrology; accepted abstract to be presented November, 2013.

- Legendre et al 2013, 'Terminal complement inhibitor eculizumab in atypical haemolytic uremic syndrome', *New England Journal of Medicine,* vol 368 (23), 2169-2181.

    - Study described as **Trial 1**

C08-003A/B:

- Clinical study report: An open-label, multi-centre controlled clinical trial of eculizumab in adult/adolescent patients with plasma therapy-sensitive atypical haemolytic-uremic syndrome (aHUS)

- Meeting abstracts:

    - Muus et al 2010. Safety & Efficacy of Eculizumab in aHUS Patients on Chronic Plasma Therapy: Interim Analysis of a Phase II Trial. American Society of Nephrology, abstract SA-PO157.

    - Licht et al 2011. Ph II Study of Eculizumab in Patients with aHUS Receiving Chronic PE/PI; American Society of Nephrology, abstract TH-PO366.

    - Licht et al 2012. Eculizumab is Effective in aHUS Patients with a Long Disease Duration and CKD: 2-year Data; American Society of Nephrology, abstract SA-OR103.

    - Licht et al 2012. Eculizumab in is Effective in aHUS patients with Long Duration of Disease and CKD: 2-year Data. American Society of Hematology, abstract 985.

    - Goodship et al 2012. Eculizumab is effective in Patients with aHUS Regardless of Underlying Genetic Mutations or CFH Auto-antibodies. American Society of Nephrology, abstract TH-PO442.

    - Delmas et al 2013. Eculizumab in aHUS Patients with Long Disease Duration and CKD: Sustained Efficacy at 3 Years. American Society of Nephrology; accepted abstract to be presented November, 2013

- Legendre et al 2013, 'Terminal complement inhibitor eculizumab in atypical haemolytic uremic syndrome', *New England Journal of Medicine,* vol 368 (23), 2169-2181.

    - Study described as **Trial 2**

C09-001r:

- Meeting abstracts:

    - Vilalta et al 2012. Eculizumab Therapy for Pediatric Patients with aHUS: Efficacy and Safety Outcomes of a Retrospective Study. European Society of Hematology, abstract 115.

    - Langman 2012. Systemic Multi-Organ Complications in aHUS: Retrospective Study in a Medical Practice Setting. European Hematology Association, abstract 490.

    - Goodship et al 2012. Eculizumab is effective in Patients with aHUS Regardless of Underlying Genetic Mutations or CFH Auto-antibodies. American Society of Nephrology, abstract TH-PO442.

<u>C10-003:</u>

- Meeting abstracts:

    - Greenbaum et al 2013. Eculizumab Inhibits TMA and Improves Renal Function in Pediatric aHUS Patients. American Society of Nephrology; accepted abstract to be presented November, 2013

C10-004:

- Meeting abstracts:

    - Fakhouri et al 2013. Eculizumab Inhibits TMA and Improves Renal Function in Pediatric aHUS Patients. American Society of Nephrology; accepted abstract to be presented November, 2013

<u>C11-003:</u>

- Meeting abstracts:
    - Licht et al, 2013. An observational, non-interventional, multicentre, multinational registry of patients with aHUS: Initial patient characteristics. Accepted abstract to be presented at American Society of Nephrology, November, 2013

Data from unpublished studies, including C10-003, C10-004, C11-003 and M11-001, have been extracted from interim clinical study reports or clinical trial protocols (Appendices 17.7). The long-term extension study, C11-003, includes patients that have participated in any previous controlled trial, including trials C08-002, C08-003, C09-001r C10-003, or C10-004.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Differences in patient populations include age, duration of disease, number of patients receiving PE/PI at screening, number of PE/PI sessions during current aHUS event, number of patients on dialysis, platelet count, and LDH at baseline (Table C8). Methodology was similar across prospective studies, while varying in observational studies, as described in Table C6 and Table C7..

Table C8: Summary of patient populations and study characteristics for key eculizumab clinical trials

Trial	N (ITT)	Age (years), Median (min; max)	Age Category				Time (mo.) from dx to screening, Median (min; max)	PE/PI sessions during current aHUS event, Median (min; max)	Dialysis at screening, n (%)	Platelet count ($x10^9$/L) at baseline, Median (min; max)	LDH at baseline, Median (min; max)
			Infant (<2 years)	Children (≥2-12)	Adolescent (≥12-≤18)	Adult (≥18)					
C08-002	17	28 (17; 68)	0	0	1	16	9.7 (0.26; 236)	17 (2; 37)[a]	6 (35)	118 (62; 161)	269 (134; 634)
C08-003	20	28 (13; 63)	0	0	5	23	48 (0.66; 286)	62 (20-230)	2 (10)	218 (105; 421)	200 (151; 391)
C09-001r	30	12 (0.17; 51.4)	5	10	4	11	10.9 (0.23; 175.9)[b]	8 (0; 29)	11 (37)[c]	159 (25; 381)	[redacted]
C10-003	22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.56 (0.03; 191.3)[d]	[redacted]	11 (50)	[redacted]	[redacted]
C10-004	41	[redacted]	0	0	0	41	0.79 (0.03; 311.26)	[redacted]	24 (59)	[redacted]	[redacted]

[a] Within 56 days of first dose
[b] At first dose
[c] Patients with at least one dialysis session
[d] duration of confirmed disease

[redacted]

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In prospective studies C08-002, C08-003, and in the retrospective study C09-001r, primary and secondary endpoints were analysed by presence or absence of complement factor mutations and auto-antibodies and prior kidney transplant or naïve kidney, history of clinical TMA manifestations. No significant differences in haematological normalization, avoidance of PE/PI or new dialysis, as well as improvement in renal function or quality of life was observed based on presence or absence of complement mutations or auto-antibodies and history of renal transplant. There was no assessment of safety or efficacy by demographic characteristics.

In prospective study C10-003 (paediatric), the primary endpoint was complete TMA response (Haematologic normalisation (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline) confirmed by two consecutive measurements obtained at least four weeks apart. The primary endpoint was achieved with significance. Specifically, 14/22 patients (64%; 95% CI: 41 - 83) achieved the high hurdle of a complete TMA response from baseline through 26 weeks. [redacted]
Whether a patient was on dialysis or not on dialysis at baseline did not have an apparent effect on the proportion of patients who achieved complete TMA response. [redacted]

[redacted] Platelet count normalization (achieved in 21/22 patients (95%;), complete haematological normalization (achieved in 18/22 patients (82%; 95% CI: 60 - 95)), and improvement in eGFR of at least 15 ml/min/1.73m^2 (achieved by 19/22 patients (86%; 95% CI: 65.1% - 97.1%)) [redacted]

In C10-004 (adult), the primary endpoint, TMA response (haematologic normalisation (platelet count and LDH) and less than 25% worsening in serum creatinine from baseline), confirmed by two consecutive measurements obtained at least four weeks apart, was achieved with significance in 30/41 patients (73%; 95% CI: 57.1-85.8). [redacted] Platelet count normalization (achieved in 40/41 patients 98%; 95% CI: 87.1-99.9)), complete haematological normalization (achieved in 36/41 patients (88%; 95% CI:)), and improvement [redacted]

[redacted]

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not applicable because patients did not enter the study randomised.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

C08-002 (Legendre et al, 2013; Trial 1)

Four patients discontinued during the 26 week study or did not continue to the extension study period as follows:

1. Protocol violation: patient diagnosed with SLE approximately one week after the first dose of eculizumab.
2. Discontinued due to an adverse event deemed not related to study drug.
3. Completed treatment period, and the investigator elected not to enrol patient in extension period.
4. Completed treatment period, and investigator elected not to enrol patient in extension period. Data were not collected during follow-up period as patient refused to continue participation.

Two patients discontinued during the extension study period as follows:

1. Adverse event ("decrease in renal function" per investigator) deemed not related to study drug.
2. Adverse event (worsening of renal function) deemed not related to study drug.

C08-003 (Legendre et al 2013; Trial 2)

One patient who completed the 26 week study period did not continue into the extension study period due to personal reasons (this patient subsequently restarted eculizumab due to declining clinical condition but this was outside of the clinical trial). One patient discontinued during the extension study period due to an AE (gastrointestinal haemorrhage leading to death) deemed not related to study drug.

C10-003, Eculizumab in Paediatric Patients with aHUS

Three patients discontinued during the 26-week study period as follows:

[redacted]

[redacted]

C10-004, Eculizumab in Adult Patients with aHUS

Three patients discontinued during the 26-week study period as follows:

[redacted]

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in Table C9 and Table C10.

Table C9 and Table C10 include critical appraisal for studies C08-002, C08-003, C09-001r, C10-003, and C10-004. Critical appraisal has not been completed for studies C11-003 (long-term extension) or M11-001 (aHUS registry) because enrolment is on-going and outcome analysis is not yet available.

Table C9 Critical appraisal of controlled trials

Study name	**C08-002, Legendre 2013, Trial 1**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	Single-arm, open-label study
Was the concealment of treatment allocation adequate?	N/A	Single-arm, open-label study
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Single-arm, open-label study
Were the care providers,	N/A	Single-arm, open-label study

Study name	C08-002, Legendre 2013, Trial 1	
participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	Single-arm, open-label study
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Exploratory endpoints as described in the clinical study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	For all efficacy endpoints, the primary analysis was based on the ITT population. Missing data were imputed by last observation carried forward method.

Study name	C08-003, Legendre 2013, Trial 2	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	Single-arm, open-label study
Was the concealment of treatment allocation adequate?	N/A	Single-arm, open-label study
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Single-arm, open-label study
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	Single-arm, open-label study

Study name	C08-003, Legendre 2013, Trial 2	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	Single-arm, open-label study
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Exploratory endpoints as described in the clinical study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	For all efficacy endpoints, the primary analysis was based on the ITT population. Missing data were imputed by last observation carried forward method.
Adapted from Centre for Reviews and Dissemination (CRD) (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	C10-003, Eculizumab in paediatric aHUS patients	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	Single-arm, open-label study
Was the concealment of treatment allocation adequate?	N/A	Single-arm, open-label study
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Single-arm, open-label study
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	Single-arm, open-label study
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	Single-arm, open-label study

Study name	C10-003, Eculizumab in paediatric aHUS patients	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Exploratory endpoints as described in the clinical study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	For all efficacy endpoints, the primary analysis was based on the ITT population. Missing data were imputed by last observation carried forward method.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	C10-004, Eculizumab in adult aHUS patients	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	Single-arm, open-label study
Was the concealment of treatment allocation adequate?	N/A	Single-arm, open-label study
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Single-arm, open-label study
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	Single-arm, open-label study
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	Single-arm, open-label study
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Exploratory endpoints as described in the clinical study report.
Did the analysis include an intention-to-treat	Yes	For all efficacy endpoints, the primary analysis was based on the ITT population. Missing data were

Study name	C10-004, Eculizumab in adult aHUS patients	
analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		imputed by last observation carried forward method.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C10: Critical appraisal of observational studies

Study name	C09-001r	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	[redacted]	[redacted]
Was the exposure accurately measured to minimise bias?	[redacted]	[redacted]
Was the outcome accurately measured to minimise bias?	[redacted]	[redacted]
Have the authors identified all important confounding factors?	[redacted]	[redacted]
Have the authors taken account of the confounding factors in the design and/or analysis?	[redacted]	[redacted]
Was the follow-up of patients complete?	[redacted]	[redacted]
How precise (for example, in terms of confidence interval and p values) are the results?	[redacted]	[redacted]
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in Table C11.

Table C11: Outcomes from published and unpublished studies

Study name	C08-002, Legendre 2013 Trial 1			
Size of study groups	Treatment	17		
	Control	n/a		
Type of analysis	Intention-to - treat/per protocol	ITT for all analyses		
Study duration	Time unit	26 weeks	64 weeks[a]	114 weeks[a]
Outcome	Name	Change in platelet count from baseline (primary endpoint)		
	Unit	x 10^9/L		
Effect size	Value	73	91	88
	95% CI	40-105	67-116[b]	63-112
Statistical test	Type	Repeated measures ANOVA		
	p value	=0.0001	<0.0001	<0.0001
Other outcome	Name	Normalization of platelet count		
	Unit	n (%)		
Effect size	Value	14 (82)	15 (88)	15 (88)
	95% CI	57-96	64-99	64-99
Other outcome	Name	TMA event-free status[c]		
	Unit	n (%)		
Effect size	Value	15 (88)	15 (88)	15 (88)
	95% CI	64-99	64-99	64-99
Other outcome	Name	TMA intervention rate, **pre-eculizumab**		
	Unit	Events/patient/day		
	median	0.88		
	range	(0.04-1.59)		
Other outcome	Name	TMA intervention rate, **during eculizumab**		
	Unit	Events/patient/day		
	median	0	0	0
	range	0-0.31	0-0.31	0-0.31
Statistical test	Type	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	p<0.0001
Other outcome	Name	CKD improvement by ≥ stage[d]		
	Unit	n (%)		
Effect size	Value	10 (59)	11 (65)	12 (71)
	95% CI	33-82	38-86	44-90
Other outcome	Name	eGFR, change from baseline		
	Unit	Mean mL/min/1.73m^2		
Effect size	Value	31	31	32[d]
	95% CI	17-45	15-46	15-49
Statistical test	Type	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	P<0.0008
Other	Name	eGFR improvement ≥ 15 mL/min/1.73m^2 [e]		

Study name	C08-002, Legendre 2013 Trial 1			
outcome	**Unit**	n (%)		
Effect size	**Value**	8 (47)	9 (53)	10 (59)
	95% CI	23-72	28-77	33-82
Other outcome	**Name**	Decrease in proteinuria by ≥ 1 grade[f]		
	Unit	n/N (%)		
	Value	12/15 (80)	9/11 (82)[g]	7/9 (78)[d]
Other outcome	**Name**	HRQoL change from baseline		
	Unit	Mean point change		
Effect size	**Value**	0.32	0.32	0.33
	95% CI	(0.27-0.38)	(0.27-0.38)	(0.30-0.36)
Statistical test	**Type**	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	p=0.001
Other outcome	**Name**	HRQoL, evaluable patients achieving MID of 0.06[e]		
	Unit	n/N (%)		
Effect size	**Value**	12/15 (80)	13/15 (76)	13/15 (76)
	95% CI	52-96	59-98	59-98
Other outcome	**Name**	Hb improvement > 20 g/L[e]		
	Unit	n (%)		
Effect size	**Value**	11 (65)	13 (76)	13 (76)
	95% CI	38-86	50-93	50-93
Other outcome	**Name**	Hematologic normalization[h]		
	Unit	n (%)		
Effect size	**Value**	13 (76)	15 (88)	15 (88)
	95% CI	50-93	64-99	64-99
Other outcome	**Name**	Complete TMA response[i]		
	Unit	N (%)		
Effect size	**Value**	11 (65)	13 (76)	13 (76)
	95% CI	38-68	50-93	50-93
Comments	a. Median duration except where noted b. Data at 60 weeks c. TMA event-free status defined as no decrease in platelet count of > 25% AND no PE/PI AND no new dialysis for ≥12 consecutive weeks d. Data at 96 weeks e. Sustained effect defined as ≥ 2 measurements over ≥ 4 weeks f. Evaluable patients g. Data at 52 weeks h. Hematologic Normalization is defined as the normalization of platelet counts and LDH levels sustained for ≥ 2 measurements over ≥ 4 weeks i. Complete TMA Response was defined as Hematologic Normalization plus improvement in renal function (25% reduction from baseline in serum creatinine, which was sustained for ≥ 2 measurements over ≥ 4 weeks).			

Study name	C08-003, Legendre 2013 Trial 2	
Size of study	**Treatment**	20

groups	**Control**	n/a		
Type of analysis	**Intention-to - treat/per protocol**	ITT for all analyses		
Study duration	**Time unit**	**26 weeks**	**62 weeks[a]**	**114 weeks[a]**
Outcome	**Name**	TMA event-free status (primary endpoint)[b]		
	Unit	n (%)		
Effect size	**Value**	16 (80)	17 (85)	19 (95)
	95% CI	59-94		
Other outcome	**Name**	Normalization of platelet count		
	Unit	n (%)		
Effect size	**Value**	18 (90)	19 (95)	18 (90)
	95% CI	68-99	75-100	68-99
Other outcome	**Name**	TMA intervention rate, **pre-eculizumab**		
	Unit	Events/patient/day		
	median	0.23		
	range	0.05-1.09		
Other outcome	**Name**	TMA intervention rate, **during eculizumab**		
	Unit	Events/patient/day		
	median	0	0	0
	range	0-0	0-0	0-0
Statistical test	**Type**	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	p<0.0001
Other outcome	**Name**	CKD improvement by ≥ stage[c]		
	Unit	n (%)		
Effect size	**Value**	7 (35)	4 (45)	12 (60)
	95% CI	15-59	23-68	36-81
Other outcome	**Name**	eGFR, change from baseline		
	Unit	Mean mL/min/1.73m^2		
Effect size	**Value**	6.1	8.3	7.1[d]
	95% CI	3.3-8.8	4.8-11.7	-0.30-14
Statistical test	**Type**	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	p<0.05
Other outcome	**Name**	eGFR improvement ≥ 15 mL/min/1.73m^2 [c]		
	Unit	n (%)		
Effect size	**Value**	1 (5)	3 (15)	8 (40)
	95% CI	0-25	3-38	19-64
Other outcome	**Name**	Decrease in proteinuria by ≥ 1 grade[e]		
	Unit	n/N (%)		
	Value	8/16 (50)	7/9 (78)[f]	
Other outcome	**Name**	HRQoL change from baseline		
	Unit	Mean point change		
Effect size	**Value**	0.12	0.13	0.14[d]

Study name	C08-003, Legendre 2013 Trial 2			
Size of study groups	Treatment	20		
	Control	n/a		
Type of analysis	Intention-to - treat/per protocol	ITT for all analyses		
Study duration	Time unit	26 weeks	62 weeks[a]	114 weeks[a]
	95% CI	0.07-0.17	0.08-0.18	0.10-0.18
Statistical test	Type	Repeated measures ANOVA		
	p value	p<0.0001	p<0.0001	p<0.0001
Other outcome	Name	HRQoL, evaluable patients achieving MID of 0.06[c]		
	Unit	n/N (%)		
Effect size	Value	12/15 (80)	13/15 (87)	13/15 (87)
	95% CI	52-96	59-98	59-98
Other outcome	Name	Hb improvement > 20 g/L[c]		
	Unit	n (%)		
Effect size	Value	9 (45)	10 (50)	13 (65)
	95% CI	23-68	27-73	41-84
Other outcome	Name	Hematologic normalization[g]		
	Unit	n (%)		
Effect size	Value	18 (90)	18 (90)	18 (90)
	95% CI	68-99	68-99	68-99
Other outcome	Name	Complete TMA response[h]		
	Unit	N (%)		
Effect size	Value	5 (25)	7 (35)	11 (55)
	95% CI	9-49	15-59	32-77
Comments	a. Median duration except where noted b. TMA event-free status defined as no decrease in platelet count of > 25% AND no PE/PI AND no new dialysis for ≥12 consecutive weeks c. Sustained effect defined as ≥ 2 measurements over ≥ 4 weeks d. Data at 96 weeks e. Evaluable patients f. Data at 52 weeks g. Hematologic Normalization is defined as the normalization of platelet counts and LDH levels sustained for ≥ 2 measurements over ≥ 4 weeks h. Complete TMA Response was defined as Hematologic Normalization plus improvement in renal function (25% reduction from baseline in serum creatinine, which was sustained for ≥ 2 measurements over ≥ 4 weeks).			

Study name	C09-001r, Retrospective Observational study	
Size of study groups	Treatment	30 (paediatric and adult patients)
	Control	n/a
Type of analysis	Intention-to -treat/ per protocol	Descriptive statistics unless otherwise noted (non-interventional study)

Study duration	Time unit	26 weeks
Outcome	Name	Platelet count normalization
	Unit	N (%)
Effect size	Value	25 (83)
Other outcome	Name	TMA event-free status[a]
	Unit	N (%)
Effect size	Value	20 (67)
Other outcome	Name	TMA intervention rate, **pre-eculizumab**
	Unit	Events/patient/day
	median	0.34
	range	0.00; 2.38
Other outcome	Name	TMA intervention rate, **during eculizumab**
	Unit	Events/patient/day
	median	0
	range	0.00; 0.41
Statistical test	Type	Signed-rank test
	p value	p<0.0001
Other outcome	Name	eGFR improvement ≥ 15 mL/min/1.73m^2
	Unit	N (%)
Effect size	Value	11 (37)
Other outcome	Name	Hb improvement > 20 g/L
	Unit	N (%)
Effect size	Value	13 (43)
Other outcome	Name	Complete TMA response[b]
	Unit	N (%)
Effect size	Value	10 (33.3)
Comments	a. TMA event-free status defined as no decrease in platelet count of > 25% AND no PE/PI AND no new dialysis for ≥12 consecutive weeks b. Sponsor assessment. − Complete TMA response defined as hematologic normalization and improvement in renal function defined as ≥ 25% decrease in serum creatinine from baseline. − Hematologic normalization defined as normalization of platelet count and LDH in patients who had abnormal platelet counts at or immediately prior to baseline (LDH criterion waved if not reported during eculizumab treatment)	

Study name	C10-003, Eculizumab in Paediatric Patients with aHUS; *INTERIM ANALYSIS*	
Size of study groups	Treatment	22[a] unless otherwise noted
	Control	n/a
Type of analysis	Intention-to -treat/ per protocol	[redacted]

Study duration	[redacted]	26 weeks unless otherwise noted	[redacted]

Study name	**C10-003, Eculizumab in Paediatric Patients with aHUS; *INTERIM ANALYSIS***		
Size of study groups	**Treatment**	22[a] unless otherwise noted	
	Control	n/a	
Type of analysis	**Intention-to -treat/ per protocol**	[redacted]	
Study duration	[redacted]	26 weeks unless otherwise noted	[redacted]
Outcome	**Name**	Complete TMA response[b]	
	Unit	n (%)	
Effect size	**Value**	14 (64)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	Complete hematologic response[c]	
	Unit	n (%)	
Effect size	**Value**	18 (82)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	eGFR improvement ≥ 15 mL/min/1.73m^2 [d]	
	Unit	N (%)	
Effect size	**Value**	19 (86)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	Serum creatinine decrease ≥ 25% from baseline[d]	
	Unit	N (%)	
Effect size	**Value**	16 (73)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	Platelet count normalization[d]	
	Unit	n (%)	
Effect size	**Value**	21 (96)	[redacted]
	95% CI	[redacted]	[redacted]
Other	**Name**	[redacted]	

Study name	**C10-003, Eculizumab in Paediatric Patients with aHUS; *INTERIM ANALYSIS***		
Size of study groups	**Treatment**	22[a] unless otherwise noted	
	Control	n/a	
Type of analysis	**Intention-to -treat/ per protocol**	[redacted]	
Study duration	[redacted]	26 weeks unless otherwise noted	[redacted]
outcome	**Unit**	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Comments	[redacted]		

Study name	**C10-004, Eculizumab in Adult Patients with aHUS; *INTERIM ANALYSIS***		
Size of study groups	**Treatment**	41[a] unless otherwise noted	
	Control	n/a	
Type of analysis	**Intention-to -treat/ per protocol**	[redacted]	
Study duration	**Time unit**	26 weeks unless otherwise noted	[redacted]

Study name	**C10-004, Eculizumab in Adult Patients with aHUS; *INTERIM ANALYSIS***		
Size of study groups	**Treatment**	41[a] unless otherwise noted	
	Control	n/a	
Type of analysis	**Intention-to -treat/ per protocol**	[redacted]	
Study duration	**Time unit**	26 weeks unless otherwise noted	[redacted]
Outcome	**Name**	Complete TMA response[b] with preservation of renal function	
	Unit	n (%)	
Effect size	**Value**	30 (73)	[redacted]
	95% CI	[redacted]	[redacted]
Outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	Complete hematologic response[d]	
	Unit	n (%)	
Effect size	**Value**	36 (88)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	eGFR improvement ≥ 15 mL/min/1.73m^2 [e]	
	Unit	N (%)	
Effect size	**Value**	22 (54)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]

Study name	**C10-004, Eculizumab in Adult Patients with aHUS; *INTERIM ANALYSIS***		
Size of study groups	**Treatment**	41[a] unless otherwise noted	
	Control	n/a	
Type of analysis	**Intention-to -treat/ per protocol**	[redacted]	
Study duration	**Time unit**	26 weeks unless otherwise noted	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	Platelet count normalisation[e]	
	Unit	n (%)	
Effect size	**Value**	40 (98)	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Other outcome	**Name**	[redacted]	
	Unit	[redacted]	
Effect size	**Value**	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
Comments	[redacted]		

9.6.2 Justify the inclusion of outcomes in Table C11 from any analyses other than intention-to-treat.

All analyses in Table C11 included the respective intention-to-treat populations with the exception of:

- C08-002 and C08-003:
  - improvement in proteinuria by ≥ 1 grade was analysed in evaluable patients with ≥ grade 1 proteinuria at baseline
  - Improvement of HRQoL by MID (minimally improved difference) was analysed in evaluable patients with score ≥ 0.06 at baseline

[redacted]

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse event data from relevant and appraised studies were identified using the search strategy for clinical evidence as described in Appendices 17.1 and 17.2. Safety data for studies appraised in Sections 9.5 and 9.6 have been extracted from clinical study reports for the respective studies.

9.7.2 Provide details of all important adverse events reported for each study.

Adverse events (AEs) are reported as extracted from the respective clinical study report. Due to lack of RCT trials, AEs are reported in eculizumab-treated patients only treatment. Tables include treatment emergent adverse events (TEAEs) occurring in at least one patient by system organ class and by preferred term, that are deemed related to eculizumab. Complete AE listings are available in the respective clinical study report.

Study C08-002 (Legendre 2013, Trial 1)

Of the 10 patients (59%) who reported TEAEs that were judged to be related to eculizumab, at least 1 TEAE of moderate severity was reported in 6 patients (35%) and at least 1 TEAE of mild severity was reported in 3 patients (18%) (Table C12). A severe eculizumab-related TEAE was reported in one patient (hypertension) between Days 45 and 48 of the study that was possibly related to eculizumab and resolved. No deaths were reported during the 26-week study.

Table C12: TEAEs related to eculizumab by system organ class and preferred term and by severity, Study C08-002 (Legendre 2013, Trial 1)

System Organ Class Preferred Term	Total (N=17)	N (%)		
		Mild	Moderate	Severe
Number of Patients with at Least 1 Relationship Adverse Event	10 (59)	3 (18)	6 (35)	1 (6)
Number of Patients with No Relationship Adverse Event	7 (41)			
Blood and Lymphatic System Disorders	2 (12)	2(12)	0 (0)	0 (0)
Leukopenia	2 (12)	2(12)	0 (0)	0 (0)
Gastrointestinal Disorders	2 (12)	2(12)	0 (0)	0 (0)
Diarrhoea	1 (6)	1 (6)	0 (0)	0 (0)
Nausea	2 (12)	2(12)	0 (0)	0 (0)
Vomiting	2 (12)	2(12)	0 (0)	0 (0)
General Disorders and Administration Site Conditions	2 (12)	1 (6)	1 (6)	0 (0)
Asthenia	1 (6)	0 (0)	1 (6)	0 (0)
Pyrexia	1 (6)	1 (6)	0 (0)	0 (0)
Infections and Infestations	3 (18)	2 (12)	1 (6)	0 (0)
Herpes zoster	1 (6)	1 (6)	0 (0)	0 (0)
Impetigo	1 (6)	0 (0)	1 (6)	0 (0)
Urinary tract infection	1 (6)	1 (6)	0 (0)	0 (0)
Investigations	2 (12)	2 (12)	0 (0)	0 (0)
Haematocrit decreased	1 (6)	1 (6)	0 (0)	0 (0)
Haemoglobin decreased	1 (6)	1 (6)	0 (0)	0 (0)
Nervous System Disorders	2 (12)	1 (6)	1 (6)	0 (0)
Headache	1 (6)	1 (6)	0 (0)	0 (0)
Tremor	1 (6)	0 (0)	1 (6)	0 (0)
Skin and Subcutaneous Tissue Disorder	2 (12)	1 (6)	1 (6)	0 (0)
Dermatitis	1 (6)	1 (6)	0 (0)	0 (0)
Erythema	1 (6)	0 (0)	1 (6)	0 (0)
Vascular Disorders	3 (18)	0 (0)	2 (12)	1 (6)
Accelerated Hypertension	2 (12)	0 (0)	2 (12)	0 (0)
Hypertension	1 (6)	0 (0)	0 (0)	1 (6)

Adverse events classified according to MedDRA Version 11.0 dictionary
Only the most severe occurrence per patient counted for each term for each category
Adverse events contributed to the summary table if they occurred on the same day as the first eculizumab dose or after

Fifteen patients (88%) reported having at least one serious AE. The most common system organ classes reported for SAEs were vascular disorders (35%), renal and urinary disorders (24%), infection and infestations (24%). With the exception of vascular disorders, these SAEs were all unrelated to eculizumab administration. The most frequently reported SAE by preferred term was renal impairment, which was unrelated to eculizumab. There were no SAEs considered by the Investigator to be probably or definitely related to eculizumab.

There was only one adolescent patient in the study. This patient reported two SAEs that were moderate and severe (back pain and cholelithiasis, respectively) and were not related to eculizumab. Overall, the AEs for this patient were mostly mild (sore throat, skin irritation,

nasal congestion and insomnia). Only a moderate AE oferythema to bilateral hand cuticles was judged to be possibly related to the study drug by the PI.

As of the 2-year data update (2012 Safety and Efficacy Update, C08-002, C08-003) drug-related AEs reported by ≥5% of patients at submission were similar to those reported at update, with no new drug-related AEs reported by ≥5% of patients.

Study C08-003 (Legendre 2013, Trial 2)

TEAEs that were deemed related to eculizumab were uncommon and reported by 6 patients (30%) (Table C13). Headache, leucopoenia and lymphopenia were the most common treatment-related AEs (2 patients, 10%) and one patient had a BK infection that was deemed possibly related to study drug and mild in severity. No deaths were reported during the 26-week study.

Table C13: TEAEs related to eculizumab by system organ class and preferred term and by severity, Study C08-003 (Legendre 2013, Trial 2)

System Organ Class	Number of Patients N (%)			
	Total N = 20	Mild	Moderate	Severe
Number of Patients With at Least 1 Treatment Emergent Adverse Event Related to Eculizumab	6 (30)	1 (5)	3 (15)	2 (10)
Number of Patients Without a Treatment Emergent Adverse Event Related to Eculizumab	14 (70)			
Blood and Lymphatic System Disorders	3 (15)	2 (10)	1 (5)	0
Abnormal clotting factor	1 (5)	1 (5)	0	0
Anaemia	1 (5)	0	1 (5)	0
Leukopenia	2 (10)	2 (10)	0	0
Lymphopenia	2 (10)	1 (5)	1 (5)	0
Ear and Labyrinth Disorders	1 (5)	0	1 (5)	0
Vertigo	1 (5)	0	1 (5)	0
Gastrointestinal Disorders	1 (5)	0	0	1 (5)
Peritonitis	1 (5)	0	0	1 (5)
General Disorders and Administration Site Conditions	1 (5)	0	1 (5)	0
Extravasation	1 (5)	0	1 (5)	0
Infection and Infestations	1 (5)	1 (5)	0	0
BK virus infection	1 (5)	1 (5)	0	0
Nervous System Disorders	2 (10)	1 (5)	1 (5)	0
Headache	2 (10)	1 (5)	1 (5)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (5)	0	1 (5)	0
Cough	1 (5)	1 (5)	0	0
Rhinorrhoea	1 (5)	0	1 (5)	0
Skin and Subcutaneous Tissue Disorders	1 (5)	1 (5)	0	0
Alopecia	1 (5)	1 (5)	0	0

System Organ Class	Number of Patients N (%)			
	Total N = 20	Mild	Moderate	Severe
Pruritus	1 (5)	1 (5)	0	0
Vascular Disorders	1 (5)	0	0	1 (5)
Vein disorder	1 (5)	0	0	1 (5)

There were no occurrences of meningococcal infection or pregnancy during the study. Five patients (25%) reported having at least one SAE. Two of these SAEs (peritonitis and vein disorder) were deemed related to eculizumab treatment, had resolved by the data cut-off date, and both patients were continuing eculizumab treatment. All other SAEs were not related to eculizumab and had resolved by the data cut-off date.

As of the 2-year data update (2012 Safety and Efficacy Update, C08-002, C08-003) drug-related AEs reported by ≥5% of patients at submission were similar to those reported at update, with no new drug-related AEs reported by ≥5% of patients.

Study C09-001r, Retrospective trial

A total of 22 (73%) patients reported at least one AE in this retrospective trial (Table C14). None of the 30 patients discontinued the retrospective trial due to drug-related AEs. In addition, none of the patients experienced meningococcal infections during the eculizumab treatment period.

There were two (7%) deaths in this retrospective trial related to cerebrovascular accident (stroke) and fatal carotid artery dissection determined by the investigator to be unrelated to eculizumab.

Table C14: Summary of AEs reported by ≥10% of patients in study C09-001r

Adverse Events	Number of Patients N = 30 (%)
Number of Patients With at Least 1 Adverse Event	22 (73)
Number of Patients with No Adverse Event	8 (27)
Infection and Infestations	18 (60)
Upper respiratory tract infection	6 (20)
Influenza	3 (10)
Nasopharyngitis	3 (10)
Gastrointestinal Disorders	13 (43)
Diarrhoea	8 (27)
Vomiting	7 (23)
Nausea	3 (10)
Abdominal pain	3 (10)
General Disorders and Administration Site Conditions	12 (40)
Pyrexia	9 (30)
Respiratory, Thoracic and Mediastinal Disorders	11 (37)
Cough	7 (23)

Adverse Events	Number of Patients N = 30 (%)
Nasal congestion	4 (13)
Nervous System Disorders	11 (37)
Headache	5 (17)
Psychiatric Disorder	7 (23)
Insomnia	3 (10)
Cardiac Disorders	6 (20)
Tachycardia	4 (13)
Blood and Lymphatic System Disorder	6 (20)
Anaemia	3 (10)

(%) Percentages are based on the total number of patients. Only one occurrence per patient was counted for each preferred term.

[redacted]

[redacted] There were no deaths in this study.

[redacted]

[redacted]

[redacted]. Two (5%) of 41 patients in this study reported one meningococcal infection, for which one of these patients led to permanent discontinuation of eculizumab and withdrawal from the study, and the other continued on eculizumab treatment. Both SAEs resolved with treatment. There were no deaths in this study.

[redacted]

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Safety Overview

Eculizumab is generally very well tolerated. Although almost all patients reported adverse events (AEs) in the aHUS studies, few were considered drug-related by the investigators. In the two prospective studies, there was only one AE which led to treatment discontinuation,

and this AE was deemed unrelated to study drug. Although there were two deaths in the aHUS retrospective study, neither was considered drug-related.

The AE profile with eculizumab treatment of aHUS patients is consistent with the safety profile with eculizumab previously reported in PNH patients. Most AEs with eculizumab in aHUS were not considered drug-related and most were mild in severity. There were no identifiable trends in AE reporting among different age groups, including paediatric patients, or other subpopulations identified for analysis.

There were no reported meningococcal infections with eculizumab treatment of aHUS patients in the prospective controlled studies (C08-002 or C08-003), or in the retrospective study (C09-001r). There was a single meningococcal infection reported in an aHUS patient, which occurred in a patient included in study C09-001r after the data cut-off and was captured as a post-marketing report. This patient fully recovered without sequelae and remained on eculizumab. Two meningococcal infections have been reported in on-going trial C10-004. Both infections resolved with appropriate treatment, although one led to study withdrawal. There did not appear to be evidence for an increased risk of other serious infections with eculizumab treatment, similar to observations in PNH.

Longer-term eculizumab treatment was well tolerated and the number of AEs decreased with on-going treatment. No cumulative toxicity of therapy or serious infection-related AEs, including meningococcal infections, were observed through the extension periods in the studies described.(Legendre et al, 2013) As expected, during longer exposure, the number of patient reports of the most commonly reported AEs appears to increase, particularly in the C08-003A/B study population with long duration of aHUS, although it is noted that the majority of AEs described in the updated report are non-serious, and easily managed in clinical practice. The relationship with eculizumab is difficult to establish, as no direct comparison exists. Some of the AEs may be influenced by other baseline concomitant medications such as immunosuppressants.

Discontinuation of eculizumab

Study observations indicate that discontinuation of chronic complement inhibition therapy in a disease characterized by life-long uncontrolled complement activation and subsequent systemic TMA exposes patients to the risk of severe and life-threatening TMA complications. Severe TMA complications were observed after eculizumab discontinuation in the aHUS clinical studies. Because of the life-long uncontrolled complement activation in patients with aHUS and the role of eculizumab treatment to inhibit this otherwise uncontrolled complement activation, it is important to understand the identified risk of severe TMA complications in aHUS patients discontinuing eculizumab.

In the 67 patients recruited within the registration prospective and retrospective trials, there were 18 instances of eculizumab discontinuation. Importantly, 13 occurred within the non-controlled treatment setting of the retrospective trial. Following discontinuation of eculizumab treatment, there were seven severe TMA complications. Reported medical complications associated with these severe TMA complications included graft failure requiring haemodialysis, renal insufficiency, ESRF, respiratory distress requiring intubation, diarrhea and increased renal insufficiency, and nephrotic syndrome and renal insufficiency.

As highlighted in Table C15 below, in the two prospective studies, five patients discontinued eculizumab—one due to meeting an exclusion criterion, one due to an adverse event unrelated to eculizumab treatment, and three patients chose not to continue treatment in the extension phase following completion of the 26-week treatment period. In the prospective

studies, 32 of 37 patients (87%) continued to receive long-term treatment during the extension phase.

Table C15: Severe TMA Complications in Patients Discontinuing Eculizumab

Reason for Discontinuation	No. of Patients	No. of Patients with Severe TMA Complications
Eculizumab stopped by investigator due to perceived lack of quick response of renal improvement (regardless of impact on TMA)	5	2
Eculizumab stopped early following normalized renal and/or hematologic function	4	2
Patient chose not to participate in extension of prospective study	3	1
Death unrelated to drug*	2	-
Severe TMA complication concomitant with viral infection	1	-
Administrative reason	1	-
Met study exclusion criteria	1	-
Adverse event unrelated to drug	1	-

*Both deaths were reported in patients enrolled in the retrospective study. One patient died following carotid artery surgery, which had been undertaken due to severe diffuse arterial stenosis reported to be due to TMA. The other death occurred due to Graft versus Host Disease in a patient who had undergone bone marrow transplantation for a concomitant disease.

It is important to note that the median duration of follow-up of these 18 patients who discontinued therapy was 27 days and only 3 patients had longer than 8 weeks follow-up. From the available follow-up period, the following information was observed:

- Five patients (28%) experienced severe TMA complications:
  - Four of the five patients subsequently re-initiated eculizumab treatment
- Four patients (22%) did not have follow-up:
  - Of these, two patients died, one was lost to follow up, and one was excluded fro m the study.
- Five patients (28%) were on dialysis before and after eculizumab treatment:
  - The maximum follow-up for these patients was 24 days, and
  - Occurrence of TMA and extra-renal symptoms is not known.
- Four patients (22%) had no complications reported by the end of data collection:
  - The median follow-up for these patients is 50 days, ranging from 42 to 241 days .

Interim analysis of prospective trial C10-003 in paediatric aHUS patients reports three discontinuations before completion of the 26-week treatment period. [redacted]

Three patients were withdrawn from trial C10-004 (adult patients) prior to the completion of the 26-week treatment period. [redacted]

Collectively, these observations indicate that discontinuation of complement inhibition in a disease characterized by life-long, uncontrolled complement activation and subsequent TMA with life-threatening organ complications can lead to a loss of inhibition of the TMA process and life-threatening medical complications. Moreover, the European Commission, in the eculizumab SmPC, has concluded that eculizumab treatment is recommended to continue for the patient's lifetime, unless the discontinuation of eculizumab is clinically indicated for safety considerations.

*9.8 **Evidence synthesis and meta-analysis***

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Studies C08-003 and C08-002, described in detail within this submission, enrolled patients with different clinical characteristics. Study C08-003 included patients with long duration of aHUS, prolonged PE/PI exposure and substantial kidney damage, whereas C08-002 included patients with progressing TMA and shorter disease duration. These trials demonstrated the efficacy of eculizumab in a broad range of aHUS patients, reflective of the addressable population. However, this does not lend itself to metaanalysis and would not provide results which are more informative than those included within the submission document. Due to the lack of RCTs and the heterogeneity of patients included in the non-randomised prospective and observational trials included in this submission, evidence synthesis or meta-analysis were not performed.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

As detailed above, a metaanalysis is not considered to be appropriate. Studies C08-003 and C08-002 demonstrated the efficacy of eculizumab across a broad range of aHUS patients to:

- Inhibit complement activation in all treated patients;
- Inhibit complement-mediated TMA;
- Significantly improve renal function (including removal of dialysis in C08-002);
- Prevent disease progression (including avoidance of dialysis);
- Eliminate need for burdensome PE/PI;
- Improve systemic organ function (including brain, gastrointestinal tract as described in the case reports below);
- Significantly improve HRQL; and
- Be well-tolerated

The studies recruited patients diagnosed with aHUS and utilised a range of endpoints designed to capture the impact of eculizumab on the clinical course of aHUS. A single arm design was utilised due to the extremely rare prevalence of aHUS, the challenge of recruiting patients with this ultra-rare disease, and the prior publication of several case reports strongly indicating a therapeutic benefit of eculizumab in a small number of aHUS patients.

Legendre et al. 2013 undertook an analysis to confirm the treatment effect utilising pre-treatment data as within patient controls. In both trials, the rate of intervention for thrombotic microangiopathy, comprising plasma exchange/infusion and dialysis was significantly lower during the period of eculizumab treatment than during the period before treatment. The authors noted that this highlighted the inadequate efficacy of management with plasma exchange or infusion and confirmed the clinically relevant treatment effect of eculizumab on thrombotic microangiopathy and organ outcomes (Legendre et al, 2013). Similar analysis of renal function before and during eculizumab treatment shows a striking improvement in renal function upon discontinuation of PE/PI and initiation of eculizumab in both studies.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Use of Eculizumab in aHUS

In contrast to PE/PI, eculizumab is designed to directly and potently block activation of the terminal stage of the complement system and inhibit chronic uncontrolled complement activity, inflammation, and systemic complement-mediated TMA in patients with aHUS.(Rother et al, 2007) As a result, use of eculizumab reduces the underlying TMA process and subsequently can reverse or prevent further kidney damage, allowing aHUS patients to discontinue or avoid dialysis. Eculizumab also prevents progression of other organ damage in aHUS patients, removes the need for PE/PI, and dramatically improves patients' quality of life.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011) These benefits were demonstrated in two prospective controlled clinical trials and a retrospective analysis involving a broad range of aHUS patients, including patients of all ages. When compared to the natural progression of the disease and historically poor outcomes at one year, these trials provide for the first time a proven, effective, and safe first-line treatment for aHUS patients.(Gruppo and Rother, 2009; Legendre et al, 2010; Muus P et al, 2010; Davin et al, 2010; Lapeyraque et al, 2011) Put simply, eculizumab treatment in aHUS patients changes the course of the disease and leads to substantial and demonstrable gains in patient outcomes.

On September 23, 2011, the United States Food and Drug Association (FDA) approved eculizumab for the treatment of children and adults with aHUS to inhibit systemic complement-mediated TMA. Approval by the European Commission was obtained on November 24, 2011. In recognition of the chronic nature of aHUS and the on-going substantial risk of mortality and significant morbidities, the Soliris Summary of Product Characteristics (SmPC) states that eculizumab treatment is recommended to continue for the patient's lifetime.

In addition to aHUS, eculizumab also has been demonstrated to provide long-term safety and efficacy in the treatment of paroxysmal nocturnal haemoglobinuria (PNH), an ultra-rare and life-threatening disease that also results from chronic uncontrolled complement

activation.(FDA Prescribing Information, 2012; SmPC, 2013) Long-term inhibition of chronic uncontrolled complement activity with eculizumab in PNH patients decreases platelet consumption and thromboembolism, improves kidney function and pulmonary hypertension, and ultimately increases the overall survival from the historical rate of only 65% at five years to a survival rate that is indistinguishable from a normal age and sex-matched population.(Hillmen et al, 2007; Socie G et al, 2009; Hillmen et al, 2010; Brodsky R et al, 2010; Kelly R et al, 2011)

Results of aHUS Clinical Studies

Chronic eculizumab treatment in aHUS has been investigated in two prospective open-label, single-arm, multi-national clinical trials, and a single retrospective open-label, single-arm, multi-national clinical trial, in 37 and 30 (including 19 paediatric) aHUS patients, respectively. Two additional prospective single-arm trials are underway in adult and paediatric patients. These trials demonstrate that early and sustained blockade of chronic, uncontrolled complement activation with eculizumab stops systemic TMA and results in statistically and clinically significant restoration of kidney function and gains in health, while eliminating the need for PE/PI in patients with aHUS.(Legendre et al, 2010; Muus P et al, 2010; Greenbaum et al, 2011; Licht et al, 2011)

Prospective Study C08-003

In the prospective study C08-003 that included patients with a long duration of aHUS, chronic renal impairment, and long-term PE/PI, 100% of patients treated with eculizumab reduced their TMA intervention rate, eliminated PE/PI, and prevented the need for new dialysis. In this cohort of patients who had a long history of aHUS, substantial long-term expected permanent renal complications (50% of patients with Stage 4-5 CKD, eGFR ≤60 ml/min/1.73m^2, including chronic dialysis) and long-term supportive care (median 10 months of PE/PI prior to receiving eculizumab), it could have been anticipated that no therapeutic intervention would be able to change the course of this severe disorder. However, intervention with chronic eculizumab treatment in these patients did in fact change the course of their disease. Chronic eculizumab treatment resulted in a significant time-dependent improvement in renal function and a significant decrease in proteinuria (a measure of on-going renal impairment) at two years. Importantly, 82% of patients achieved a significant gain of health.(Legendre et al, 2013) Together, these results demonstrate the beneficial effects of eculizumab in aHUS patients with any level of organ damage and at any point of disease duration.

Prospective Study C08-002

In the prospective study C08-002, in patients with aHUS and continued platelet consumption and renal damage while receiving PE/PI, chronic eculizumab therapy normalised platelet counts in 92.3% of aHUS patients who had low platelet counts at baseline. Similarly, 100% of patients treated chronically with eculizumab achieved TMA event-free status with no new dialysis required, no need for PE/PI, and patients maintained their platelet counts through 26 weeks. In addition, 100% of patients improved or maintained their eGFR, a measure of kidney function, through 26 weeks. With long-term eculizumab therapy (median 100 weeks), 59% of patients achieved a significant improvement in eGFR (≥15 ml/min/1.73m^2). Additionally, 71% of aHUS patients (95% CI 44-90) experienced clinically important improvement in chronic kidney disease by at least one stage.(Canaud et al, 2013)

Illustrating the dramatic positive effect of eculizumab treatment in reversing failed renal function in aHUS patients, chronic eculizumab treatment allowed four of five patients who

required dialysis at study entry to permanently discontinue and eliminate dialysis. In addition, chronic eculizumab treatment also resulted in clear gains in overall health with 80% of patients (95% CI 52-96) treated with eculizumab achieving clinically meaningful improvement in quality of life at week 26 compared to baseline and increasing long-term to 87% of patients (95% CI 59-98; median 100 weeks).(Legendre et al, 2010; Alexion, 2011)

In addition to achieving clinically important endpoints, results from both prospective trials with eculizumab further demonstrate the disease-causing role of chronic uncontrolled complement activation in aHUS. This is demonstrated by the observation of significant efficacy of eculizumab treatment in patients with or without an identifiable genetic abnormality leading to complement dysregulation. In patients with short or long history of disease, overtly progressing clinical TMA or apparently irreversible organ damage, further uncontrolled complement-mediated TMA activity leads to progressive organ damage with all available supportive care. Delay in complement intervention during presentation of overtly progressing clinical TMA, or during longer-term supportive care with PE/PI, leads to progressive organ damage and reduces the ability of eculizumab to reverse organ function. Chronic inhibition of complement-mediated TMA with eculizumab treatment is recommended by the European Commission to continue for the patient's lifetime.

Retrospective Study C09-001r

This retrospective open-label, single-arm, multi-national clinical trial included 19 patients under 18 years of age (as young as two months) and 11 adult patients who received eculizumab outside of clinical trials between 2007 and 2009. The data indicate that safety and efficacy results with eculizumab in the clinical practice setting are consistent with those reported for adults and adolescents in the prospective controlled studies.(Alexion, 2011; Simonetti et al, 2011)

[redacted] In the retrospective study, 100% of paediatric patients were receiving supportive care prior to initiation of eculizumab and reduced their TMA intervention rate from a median of 0.31 to 0 interventions per patient per day (P<0.0001). Treatment with eculizumab stopped complement-mediated TMA and enabled almost all paediatric aHUS patients (17/19, 89%) to achieve normalisation of platelets. Nine of the 19 paediatric patients (47%) also experienced a clinically meaningful improvement in renal function as demonstrated by an improvement in eGFR ≥15 mL/min/1.73m^2. Importantly, four of eight (50%) paediatric patients who previously required dialysis were able to discontinue dialysis once on eculizumab treatment. Further, no paediatric patient required new dialysis during treatment with eculizumab.

Prospective Study C10-003[redacted]

This trial was an open-label, non-randomized, single-arm, multi-centre clinical trial of eculizumab in paediatric patients (one month up to 18 years) with aHUS. The study was designed to assess efficacy and safety of eculizumab in paediatric patients with aHUS to control TMA as characterized by thrombocytopenia, haemolysis and renal impairment.

[redacted] and ranged between one month to 17 years. The time from current clinical TMA complications to first dose was a median of six days, [redacted] The primary endpoint of complete TMA response was achieved with significance, 14/22 patients (64%; 95% CI: 41-83) from baseline through 26 weeks. This high threshold of response included normalization of haematological

parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Inhibition of TMA by eculizumab as measured by platelet count normalization was achieved in 21/22 patients (96%; 95% CI: 77-100), and as measured by complete hematologic response in 18/22 patients (82%; 95% CI: 60-95).

[redacted] Improvement of organ function with eculizumab treatment was achieved in 16/22 patients (73%) as measured by a reduction in serum creatinine of at least 25% compared to baseline through 26 weeks of treatment. Improvement in eGFR ≥15 mL/min/1.73m^2 from baseline through 26 weeks of treatment was achieved by 19 out of 22 patients (86%; 95% CI: 65.1%-97.1%).

[redacted] Eighty-two percent (9/11) of patients who were on dialysis at baseline no longer required dialysis during eculizumab treatment, [redacted] through the 26-week Treatment Period [redacted]

[redacted]

[redacted] Additionally, when treatment is initiated early, 9/11 patients were able to come off dialysis.

Prospective Study C10-004 [redacted]

This is an open-label, non-randomized, single-arm, multi-centre clinical trial of eculizumab in patients with aHUS that were at least 18 years of age or older. The study was designed to assess efficacy and safety of eculizumab to control TMA as characterized by thrombocytopenia, haemolysis and renal impairment. [redacted] The median time from current clinical TMA complications to first dose was 0.5 months.

The primary endpoint was achieved with significance, 30/41 patients (73%; 95% CI: 57.1-85.8) achieved the high hurdle of a modified complete TMA response from baseline through 26 weeks (normalization of haematological parameters [platelet count and LDH] and ≥ 25% improvement in serum creatinine from baseline). [redacted] Inhibition of TMA by eculizumab was measured in 40/ 41 patients (98%; 95% CI: 87.1-99.9) achieving platelet count normalization and 36/41 patients (88%; 95% CI: 73.8-95.9) achieving a complete hematologic response. [redacted]

[redacted]

Improvement of organ function with eculizumab treatment was achieved as measured by improvement in eGFR ≥15 mL/min/1.73m^2 from baseline through 26 weeks of treatment achieved by 22/41 patients (54%; 95% CI: 37.4-69.3). [redacted]

[redacted]

Two (5%) of 41 patients in this study reported meningococcal infection. One patient permanently discontinued eculizumab while the other continued on eculizumab (both SAEs resolved). [redacted]

Risks Related to Adverse Events

The blockade of terminal complement activation and the generation of C5b-9 increase the risk of meningococcal infection; therefore, use of eculizumab increases an unvaccinated patient's susceptibility to serious meningococcal infections (*Neisseria meningitides*). As indicated in the FDA-approved label and EMA SmPC, all patients must be vaccinated at least two weeks prior to receiving Soliris to reduce the risk of infection.(FDA Prescribing Information, 2012; SmPC, 2013) Patients below the age of two years and those who are treated with eculizumab less than two weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, C, Y and W135 are strongly recommended, preferably conjugated ones.

Eculizumab should not be administered to patients with unresolved *Neisseria meningitides* infection or to patients who have not been vaccinated against *Neisseria meningitides* unless they are being treated with appropriate antibiotic prophylaxis.

It is recommended that patients being treated with eculizumab be monitored for early signs of meningococcal infection. Patients should carry a safety card with them at all times.

Number Needed to Treat (NNT)

The eculizumab clinical studies were single arm studies, necessitated by the significant ethical concerns with utilizing placebo when the benefits of eculizumab had been

demonstrated in multiple case reports and the infeasibility of a randomized study in such a rare disease. Additionally, the natural history data does not report outcomes in sufficient detail to enable calculation of a number needed to treat (NNT) or number needed to harm (NNH), which is the case in any ultra-orphan disease.

An informative NNT can be generated utilizing the pre-eculizumab treatment data and endpoints during the eculizumab clinical trials. aHUS is defined by chronic uncontrolled complement activation and therefore a targeted therapy should inhibit complement activation, in order to prevent TMA. The strict composite endpoint of the effect of eculizumab to inhibit TMA and its consequences was TMA event free status which required patients to maintain their platelet count (a measure of TMA), avoid plasma exchange and not progress to require dialysis (which is the result in most patients with aHUS prior to eculizumab).

In eculizumab clinical studies C08-002 and C-08-003—in the period prior to eculizumab treatment, no patient had evidence of complement inhibition, utilizing a sensitive haemolysis assay whilst receiving plasma exchange. Across the two studies 35/37 patients had complete inhibition of complement at the primary endpoint analysis at 26 weeks. The two patients who did not achieve this by 26 weeks were the two patients who discontinued eculizumab treatment. This provides an NNT to achieve complement inhibition of 1.06, as detailed in Table C16 below:

Table C16: NNT to Inhibit Complement

	Achieved Outcome	Did Not Achieve Outcome
Treatment Group	35	2
Pretreatment Period	0	37

Control Event Rate	0
Treatment Event Rate	0.95
Absolute Risk Reduction	0.95
NNT	1.06

TMA event free status was the primary endpoint in study C08-003 and secondary endpoint in study C08-002. It is a stringent composite endpoint which measures haematological evidence of TMA (via platelet count), intervention with PE/PI, and the avoidance of the common consequence, in patients not treated with eculizumab, of reaching ESRF and dialysis. In studies C08-002 and C-08-003—in the period prior to eculizumab treatment, no patient achieved TMA event-free status. After 26 weeks of eculizumab treatment, 15/17 patients in study C08-002 had achieved TMA event-free status (the two who did not were those who discontinued treatment early), and in study C08-003 16/20 had achieved TMA event-free status (the 4 who did not had only experienced transient decreases in platelet count, but did not receive plasma exchange and did not progress to requiring dialysis. These data provide an NNT to achieve TMA event free status of 1.19, as detailed in Table C17 below:

Table C17: NNT to Achieve TMA Event Free Status

	Achieved Outcome	Did Not Achieve Outcome
Treatment Group	31	6
Pretreatment Period	0	37

Control Event Rate	0
Treatment Event Rate	0.84
Absolute Risk Reduction	0.84
NNT	1.19

The major safety consideration for eculizumab is the risk of meningococcal infection; however, no cases of meningococcal infection were reported in studies C08-002 and C08-003.

Number Needed to Harm (NNH)

The major safety consideration for eculizumab is the risk of meningococcal infection and these are observed to occur. However, no cases of meningococcal infection were reported in studies C08-002 and C08-003 and therefore an NNH has not been calculated based on the aHUS data.

Conclusion

In summary, aHUS is a devastating and life-threatening ultra-rare disease in which excessive, chronic, uncontrolled complement activation in all patients causes a life-long risk for catastrophic outcomes. Sixty-five percent of all patients die, require dialysis, or have permanent renal damage within the first year after diagnosis even when treated with any previously available supportive care including PE/PI plasma exchange and/or plasma infusion.(Neuhaus et al, 1997; Caprioli et al, 2006; Noris et al, 2010)

Chronic eculizumab therapy is the first and only proven treatment for aHUS that stops chronic uncontrolled complement activation in every treated patient and, as a result, blocks systemic TMA, reverses and prevents further kidney dysfunction, eliminates the need for new dialysis after treatment initiation, and dramatically improves patients' quality of life, all while eliminating the need for invasive and high-risk PE/PI.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The clinical trials of eculizumab are the only prospective clinical trials performed in aHUS and the first to demonstrate a well-tolerated and efficacious treatment designed to specifically inhibit complement-mediated TMA in aHUS patients. The clinical trial programme included a broad range of aHUS patients in both a prospective and medical practice setting. Patients presented with early or chronic disease, range of renal dysfunction, multiple organ damage, and PE/PI which varied in frequency and therefore represent the aHUS patient population under consideration in this appraisal.

Owing to the severe, life-threatening nature of the disease, and the evidence of efficacy from eculizumab reported in several published case studies, it is not possible to perform a randomised controlled trial, excluding critically ill patients from receiving therapy. As a result, the prospective studies are open-label, non-randomised trials. Legendre et al assessed pre-treatment data as within patient control and demonstrated in both prospective studies that the rate of plasma exchange and new dialysis was significantly lower in the pre-treatment period demonstrating the ineffectiveness of plasma exchange and the clinical efficacy of eculizumab.(Legendre et al, 2013) This was accompanied by rapid and sustained improvements in platelet count (study C08-002) and renal functions (studies C08-002 and C08-003) upon initiation of eculizumab.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical trials of eculizumab are the first prospective studies in aHUS and therefore the most relevant evidence, clearly demonstrating the efficacy and safety of eculizumab in a

broad range of aHUS patients. Eculizumab resulted in significant clinical benefit in patients immediately after presentation, as well as those with a long duration since diagnosis; patients with milder renal impairment and those with severe renal impairment; and patients with native kidney or with one or multiple prior transplants.(Legendre et al, 2013) Interim analysis demonstrates similar clinical benefit in paediatric and adult aHUS populations including patients treated without prior use of PE/PI (prospective studies C10-003 and C10-004, respectively). Meanwhile, earlier intervention with eculizumab results in greater improvement in renal function.(Legendre et al, 2013) Therefore, clear evidence has been presented demonstrating that eculizumab is the standard of care, first line treatment which should be rapidly employed in all patients diagnosed with aHUS.

Importantly, the establishment of a national specialised service utilising centre/s of expertise will serve to rapidly provide the benefit of eculizumab to all aHUS patients in England by providing fast diagnostic and management advice, including advice about the treatment of incident and prevalent cases with eculizumab.

The outcomes relative to the scope have been addressed by the clinical evidence presented (sections 9.6 and 9.9.1) as follows:

"Overall survival"

Patients with aHUS are at constant risk of premature mortality and severe morbidities due to sudden and progressive systemic complement-mediated TMA complications.(Noris et al, 2010; Taylor et al, 2010) The severity of the disease is apparent as, in the pre-eculizumab era, 33% to 40% of aHUS patients die or progress to ESRD with the first clinical manifestation. Further, 65% of all patients died, required dialysis, or had permanent renal damage within the first year of the diagnosis with all available supportive care, including PE/PI, prior to the availability of eculizumab.(Caprioli et al, 2006)

In contrast to these unacceptably high rates of death or ESRD with previously available best supportive care including PE/PI, chronic eculizumab leads to a clinically important maintenance of survival. Of 37 patients in both trials, one death (2.7%) occurred, and only two patients (5.4%) experienced worsening renal function leading to discontinuation, in all cases deemed unrelated to study drug.

"Time to disease recurrence"

Due to the underlying mechanism of disease in aHUS resulting in chronic, uncontrolled complement activation, patients are at constant risk of progressive, on-going morbidity as 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on plasma exchange or plasma infusion (PE/PI) or dialysis and a progressive increased mortality rate thereafter. Eculizumab is the only treatment that specifically blocks complement-mediated TMA and has been demonstrated in controlled, prospective trials to consistently inhibit TMA and have a positive impact on morbidity and disease progression in aHUS.

Medical evidence demonstrates that discontinuation of eculizumab or extension of dosing intervals can result in risk of TMA complications, disease progression, and end-organ damage. (Mache et al, 2009; Larrea et al, 2010; Zuber et al, 2011; Legendre et al, 2013) In prospective clinical trials (C08-002 and C08-003, Legendre 2013), 5/18 patients (28%) experienced severe TMA complications.(Legendre et al, 2013) This is evidence of the life-long risk of chronic complement activation in aHUS patients that results in risk of TMA without complement inhibition.

"Response to treatment; avoidance of dialysis; avoidance of plasma therapy; maintenance or improvement of kidney function; other major non-renal outcomes"

Prior to the availability of eculizumab 33% to 40% of aHUS patients died or progressed to ESRD with the first clinical manifestation despite the administration of PE/PI to the vast majority of these patients.(Noris et al, 2010) Further, 65% of all patients died, required dialysis, or had permanent renal damage within the first year of the diagnosis with all available supportive care, including PE/PI, prior to the availability of eculizumab.(Caprioli et al, 2006)

The clinical evidence presented demonstrates that consistently inhibits complement and TMA in a broad aHUS patient population which have been included in prospective clinical trials (C08-002, C08-003, Legendre 2013; C10-003, C10-004, Interim data analysis), regardless of age, presence of identifiable genetic complement mutation, prior or ongoing use of supportive care (dialysis or PE/PI), or history of kidney transplant. Eculizumab inhibits complement-mediated TMA similarly across patient populations, resulting in elimination of PE/PI in all patients in studies C08-002 and C08-003, with only two patients receiving any PE during the eculizumab treatment period. This demonstrates that eculizumab allows the avoidance of ineffective PE/PI. Eculizumab also improved or maintained kidney function, including removal of dialysis in some patients.(Legendre et al, 2013) Long-term eculizumab treatment is also associated with significant gains in HRQoL.

"*Eligible for/success of transplantation"*

Eligibility for or success of transplantation was not specifically addressed in the clinical trials presented. It is worth noting, however, that one patient in C08-003 with a history of five TMA clinical manifestations and chronic dialysis, received a successful kidney transplant while receiving eculizumab. This is consistent with a detailed case series reporting the effectiveness of eculizumab in preventing post-transplant TMA in aHUS and recommending eculizumab use to allow transplantation. This demonstrates eculizumab allows aHUS patients who are in ESRF to undergo kidney transplantation, in contrast to the relative contraindication to transplantation that existed prior to the availability of eculizumab (due to the unacceptably high rate of graft loss) (Zuber et al, 2012)

"Development of antibodies and resistance"

No patients in the aHUS clinical trials developed neutralizing antibodies to eculizumab. This is consistent with the significant clinical experience in PNH including the use of eculizumab for as long as 10 years. As noted in the SPC, placebo-controlled studies in PNH demonstrate that infrequent low titre antibody responses occur at similar frequencies in placebo- or eculizumab-treated patients.(SmPC, 2013) There has been no evidence of decreased efficacy and eculizumab continues to block complement activation and its consequences with long-term use.(Hillmen et al, 2013)

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

We have not identified any factors which might influence the external validity of the data provided. On-going experience since the marketing authorisation in 2011 through additional clinical trials, the aHUS registry, and anecdotal experience demonstrate that the significant efficacy and tolerability of eculizumab is reproduced in routine clinical practice.

9.9.5 Based on external validity factors identified in 9.9.4, describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The eculizumab clinical trials included a broad range of aHUS patients which is considered representative of the general population of patients in England. No criteria, beyond the clinical diagnosis of aHUS, are required to select patients who will benefit from eculizumab.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

Minimal information exists in the published literature that formally describes quality of life in aHUS patients. Information in this section is based upon feedback sought on this topic from clinical experts during the survey undertaken for this submission, along with morbidity and quality of life information described in Sections 6 and 7.

As described in Section 7, the principle aspects of aHUS that affect patients' quality of life are:

Premature death	
Disease symptoms impairing quality of life	• Kidney disease • Central nervous system symptoms • Gastrointestinal symptoms • Cardiovascular symptoms • Pulmonary symptoms
Standard of care treatment related causes of quality of life impairment	• Plasma exchange or plasma infusion • Dialysis • Transplantation • Transplantation failure

While there are no published data on which to weight the relative importance of each of these elements to the total quality of life impairment, the clinical experts interviewed felt that the majority of quality of life burden was explained by three elements: the worsening of patients kidney status and associated morbidity; the common patient need for dialysis; and the burden of plasma exchange (these are discussed in more detail in Section 7).

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Little information in the published literature exists that describes the lifetime trajectory of aHUS patient quality of life for individuals. The paucity of information that does exist relates to the course of treatment with the current standard of care, prior to the availability of eculizumab. The pattern described in this section reflects feedback sought on this question from clinical experts during the survey undertaken for this submission, along with morbidity and quality of life information described in Sections 6 and 7.

At the point of presentation, patients are usually seriously ill, potentially with renal failure, symptoms of TMA (e.g., thrombocytopenia, declining platelet count, microangiopathic haemolysis), and sometimes with other serious morbidities such as a stroke. Patients managed with current standard of care undergo daily plasma exchange, including 3 to 4 litres of whole plasma exchanged in adults or 1.5 times the entire body supply of plasma in children. Plasma exchange is associated with very poor quality of life, for reasons described in Section 7, as well as common and severe adverse events. Daily sessions are routine for two weeks, followed by several times per week.(Ariceta et al, 2009)

In the presentation phase, patients receive intensive plasma exchange. Patients are likely to require on-going plasma exchange in an attempt to slow the disease course. Chronic plasma exchange therapy may include multiple sessions per week for months or years. Despite this, patients' renal function is likely to deteriorate further over time, with the associated reduction in quality of life seen in patients in worse CKD stages (see Section 7).

According to expert feedback, approximately 60% of patients will be in ESRF after 2 years, despite receiving plasma exchange. In the literature, Caprioli et al (2006) reported approximately 33% of patients reach ESRF or die following the first clinical presentation of TMA (assumed to be within one 1 year) and Noris et al (CJASN 2010) reported approximately 56% reach ESRF or die at 3 years.(Caprioli et al, 2006; Noris et al, 2010) Fremeaux-Bacchi et al. (2013) report 56% of adults and 29% of children require renal replacement or died within 1 year of follow-up.(Fremeaux-Bacchi et al, 2013) The requirement to undergo dialysis three times per week is highly deleterious to quality of life for aHUS patients, preventing them from undertaking education or employment, and potentially infringing on their ability to create a family or enjoy leisure time.

Transplantation is an option for some patients, but the graft failure rate is high.(Legendre et al, 2013) Patients who have a successful transplant are likely to experience an improvement in quality of life as long as the graft survives. Experts noted that a 'good' outcome from transplantation might be 10 years of graft survival; therefore, even for the small proportion of aHUS patients who achieve that outcome, it is unlikely to result in a lifelong improvement in quality of life given the relatively young patient population. Patients who have an unsuccessful transplant are likely to experience worse quality of life than similar patients on dialysis who have not been transplanted.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-consequences analysis.
- Results with confidence intervals.

Health-related quality of life (HRQL) was measured in the two prospective studies of eculizumab in aHUS (C08-002 and C08-003), which are detailed in this submission. HRQL was measured using the EuroQoL Group 5-Dimension Self-Report Questionnaire [EQ-5D]. Patients completed the EQ-5D questionnaires frequently included at baseline, Day 182, and Day 364.

Eculizumab was associated with a significant improvement in HRQL. In study C08-002 the mean increase in the EQ-5D score at week 26 was 0.32 (95% CI, 0.24 to 0.39; P<0.001) and in C08-003, it was 0.10 (95% CI, 0.05 to 0.15; P<0.001) (See Figure C1 below).

The clinically meaningful threshold of 0.06 was exceeded in 87% of patients in C08-002 and in 73% of patients in C08-003 throughout the treatment period.

In C08-002, effect sizes were large (1.1 at week 26 and 0.8 through a median duration of 64 weeks). In C08-003, effect sizes were moderate (0.6 through week 26 and a median duration of 62 weeks, respectively) (See Figure C2 below).

The quality of life data collected in studies C08-002 and C08-003 adhered closely with requirements of the Reference Case. Measurement of changes in health-related quality of life were reported directly from patients using the EQ-5D, the preferred measure of health-related quality of life specified in the Reference Case. The utility scores derived from these changes (summarised in Legendre 2013 and above) were based societal preferences estimated from a US population using the time trade-off (TTO) methodology. These have subsequently been recalculated using the UK tariff for the purpose of the NICE submission (revised numbers are presented in Section 10.1.9).

HRQL measurements versus baseline at each observation period appear in Figure C3 and Figure C4 below. The statistical difference versus baseline is apparent within the first month, despite the small sample sizes. The approximately maximal effect is apparent as early as the end of month three in the C08-003 trial and before the end of month one in the 002 trial, and is sustained through the measurement period.

Figure C3: EQ-5D scores (US Tariff) from baseline to day 364 in C08-002

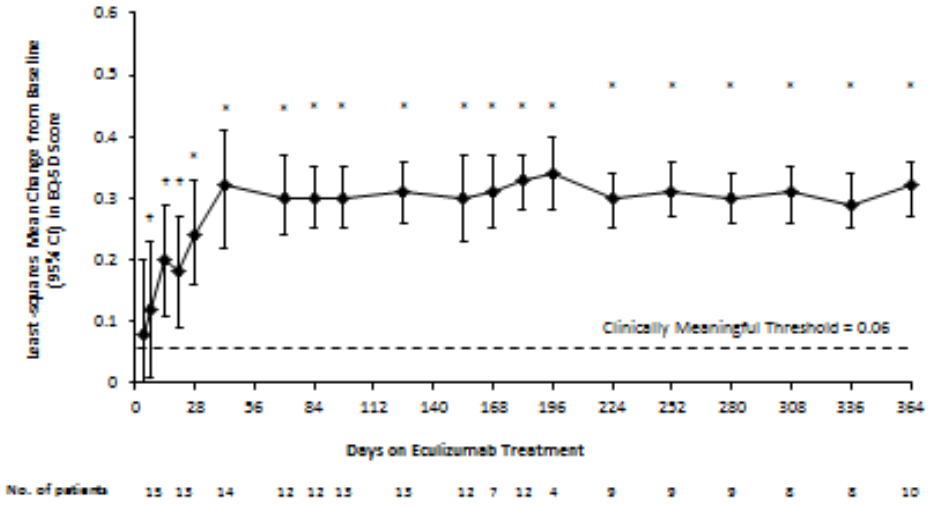
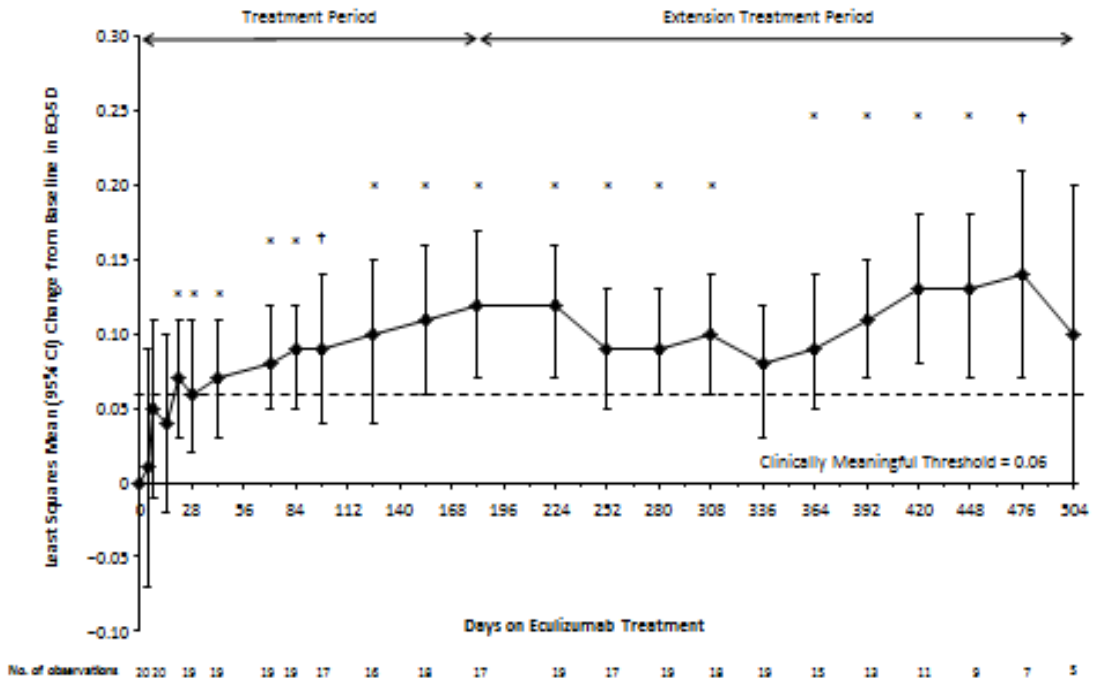


Figure C4: EQ-5D scores (US Tariff) from baseline to day 364 in C08-003



These HRQL results are relevant for the cost consequences analysis given that the analysis uses the trial populations to measure effects, which is the source of the HRQL data.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was used to transform utility or quality of life data from the eculizumab clinical trials. EQ-5D utilities were originally estimated using the US societal tariff, but these were recalculated using the UK tariff for the purpose of the NICE submission.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic review was undertaken to support the creation of the model described in Section 12. The literature review was specific to aHUS. Given the very small body of

published evidence in this disease, a broad search was undertaken to obtain the following information:

- Information on resource use and costs in aHUS,
- Economic studies in aHUS, and
- Quality of life data in aHUS.

The search strategy and study extraction tables are listed in Appendix 17.3.

The only studies found that reported quality of life data in aHUS were those reporting results from the C08-002 and C08-003 trials.(Muus et al. 2011; Legendre et al. 2013) The quality of life results presented in these papers are described in Section 10.1.3

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

The only quality of life data identified in the literature review was that reported from the eculizumab clinical trials C08-002 and C08-003. Details of these studies are described in Section 9.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The only quality of life data identified in the literature review was that reported from the eculizumab clinical trials, and as such there are no differences between the values derived from the clinical trials and those in the literature.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

As detailed in section 8.3 plasma exchange/infusion is associated with significant safety concerns. In a cohort of 249 adult TMA patients treated with plasma exchange, 26% of patients experienced major complications including:

- death in 3% of patients,
- systemic infection in 12% of patients,
- non-fatal cardiac arrest in 1% of patients,

- hypotension requiring vasopressor treatment in 3% of patients, and
- thrombosis in 2% of patients.(George, 2010)

The rate of significant safety concerns is also strikingly high in children receiving apheresis.(Michon et al, 2007) Adverse events (AEs) experienced by children included hypotension requiring fluid resuscitation (48%), hypocalcaemia (64%), severe anaemia (48%), and allergic reactions (24%). Additional safety concerns due to venous access have been reported in children receiving apheresis, including catheter-related infections (16%), catheter-related thrombosis (12%), and central venous obstruction (20%).(Michon et al, 2007)

The extensive and common AEs associated with plasma exchange significantly impair HRQL. No data have been identified exploring the impact of plasma exchange on quality of life in aHUS patients, however clinical experts interviewed for this submission consistently felt that the improvement in EQ-5D utility seen from baseline in the eculizumab clinical trials is partly explained by patients no longer needing plasma exchange, which experts felt serious impacted quality of life.

Eculizumab has been demonstrated to be well-tolerated with long-term administration in both PNH and aHUS. The principal safety concern is an increased risk of meningococcal infection and steps are taken in all patients to minimise this risk. As indicated in the SmPC, all patients must be vaccinated at least two weeks prior to receiving eculizumab to reduce the risk of infection. Patients below the age of two years, and those who are treated with eculizumab less than two weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, C, Y and W135 are strongly recommended, preferably conjugated ones.

In the aHUS clinical trials most AEs were considered to be mild to moderate in severity, as described in Section 9.7.

The demonstrated good tolerability profile of eculizumab is anticipated to have minimal impact on HRQL, as evidenced by the high quality of life scores for patients on eculizumab in C08-002 and C08-003. Furthermore, no patient in the either studies discontinued treatment due to an AE considered related to eculizumab.

Quality-of-life data used in cost-consequences analysis

10.1.9 Please summarise the values you have chosen for your cost-consequences analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Table C18: Summary of quality-of-life values for cost-consequences analysis

State	Utility value	Sample size, Std Dev	Reference in submission	Justification
Eculizumab Health State Utility				
ecu + CKD 0, 1, 2	1	0	Derived from studies C08-002 and C08-003	Weighted (by sample size) mean utility score at day 364 across both studies. These utility values represent the quality of life of aHUS patients on eculizumab
ecu + CKD 3, 4	0.870	0.189		
ecu + ESRF	0.867	0.18		

State	Utility value	Sample size, Std Dev	Reference in submission	Justification
				at the last time point at which data was collected.
Eculizumab utility benefit				
Health utility increase from Ecu across all CKD states	0.208	N=37	Legendre et al. 2013	Weighted (by sample size) improvement in mean utility score from baseline to week 64 across both studies. This is the improvement seen from eculizumab over the course of treatment, from baseline (when patients were receiving standard of care).
aHUS (SOC) Health Utility				
CKD 0, 1, 2	0.792	0.22	Derived from studies C08-002 and C08-003	Eculizumab health state utility scores minus eculizumab utility benefit.
CKD 3, 4	0.662	0.345		
ESRD	0.659	0.343		
Other states				
Post-transplant	0.662	0.345	Assumed to be equivalent to CKD 3a. See section 12.2.1, and Marcen et al NDT 2010.	In one large study evaluating 4,488 graft recipients with no aHUS, the mean eGFR was 51.2 ml/min/1.73m^2 at 3 months following transplantation and 60% of patients had CKD stage 3 at 12 months following transplantation.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Utility values used in the model were derived wherever possible from the EQ-5D data collected in the eculizumab clinical trial programme. Experts were therefore not used for the purpose of utility value estimation; however, experts did provide general qualitative feedback on the quality of life of patients with aHUS both on SOC and eculizumab.

The process by which expert involvement was obtained is described in Section 12.2.5.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

In aHUS, quality of life is expected to deteriorate over time for patients treated with SOC prior to eculizumab. This deterioration is reflected in the model by deterioration in patient eGFR status and the subsequent transition to more serious CKD stages, including ESRF, which in turn are associated with lower quality of life. However, quality of life is assumed to stay constant within individual health states for patients in SOC and eculizumab. The difference in SOC and eculizumab health state health utility is based on the trial observations and assumed to be due to SOC patients continuing to have a complement disorder, TMAs, and to be undergoing SOC treatment including plasma exchange.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

As described in Section 6, the manifestation of aHUS is heterogeneous with many organ systems involved. A primary driver of morbidity is through kidney disease, as reflected in the model. However, other manifestations occur due to TMAs including neurological complications, cardiovascular disease, thrombosis, gastrointestinal disorders and pulmonary symptoms. These were excluded from the model due to the lack of published data on the frequency and impact of these events, and based upon feedback from clinical experts. These symptoms are most likely associated with TMA incidence which was significantly reduced from baseline in patients treated with eculizumab in C08-002 and C08-003 trials. Excluding the quality of life impact of TMA events in the model therefore represents a conservative assumption.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients are allocated to CKD states at the beginning of the model based upon the distribution of patient CKD stages in studies C08-002 and C08-003. Each CKD state is associated with its own health utility.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Quality of life is assumed to remain constant over time within health states, although patients treated with SOC will experience deterioration in eGFR that translates to more serious CKD stages and subsequently lower quality of life. Quality of life is assumed to stay constant within individual health states for patients in SOC and eculizumab. Please see Section 10.1.11 for more detail.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Utility values have been taken directly from either the eculizumab clinical trials or from estimates from published literature.

For the health states CKD 0-1-2, CKD 3a-3b-4, and ESRF, EQ-5D estimates from C08-002 and C08-003 were used corresponding to those states. Eculizumab values are those at week 52 in the trial. We use the published difference in baseline and week 64 from Legendre et al. 2013 (0.208) to parameterize the utility difference for SOC patients. Please see section 12.5.3 for more detail.

Other health utilities are taken directly from the literature.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Medical evidence demonstrates that despite the use of supportive care, there is a progression of aHUS, continued on-going risk of TMA, and life threatening complications for aHUS patients.(Noris and Remuzzi, 2009; Noris et al, 2010; Hovinga et al, 2010; Legendre et al, 2013; SmPC, 2013) Eculizumab is recommended and approved to continue as a chronic treatment for this chronic disease.(SmPC, 2013) The prospective clinical trials demonstrate that chronic treatment with eculizumab can continue to improve renal function and patients' quality of life even after one year of chronic treatment. Indeed, several patients report recurrence of continued evidence of complement-mediated TMA after discontinuing eculizumab treatment, which further strengthens the evidence for the need of chronic eculizumab treatment.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

A systematic review was undertaken to support the creation of the model described in Section 12. The literature review was specific to aHUS. Given the extremely small body of published evidence in this disease, a broad search was undertaken to obtain the following information:

- Information on resource use and costs in aHUS
- Economic studies in aHUS
- Quality of life data in aHUS

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

The following electronic databases were searched:

- PubMed
- EMBASE
- Web of Knowledge
- Scopus
- CINAHL
- 'Biological Abstracts':
- EconLit
- NHS EED
- NHS HTA

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

As noted in Section 11.1 above, systematic review was undertaken to support the creation of the eculizumab submission. The literature review was specific to aHUS. Given the extremely small body of published evidence in this disease, a broad search was undertaken to obtain the following information:

- Information on resource use and costs in aHUS,
- Economic studies in aHUS, and
- Quality of life data in aHUS.

The search criteria, search results and extraction tables are included in Appendix 17.3, while the search criteria can be found in Table D1.

Table D1: Selection criteria used for health economic studies

Inclusion criteria	
Population	aHUS patients
Interventions	Any
Outcomes	Any economic, quality of life or resource use outcomes
Study design	Any
Language restrictions	English
Search dates	From database inception to 1 August 2013
Exclusion criteria	
Population	Non-aHUS populations
Interventions	None
Outcomes	None
Study design	None
Language restrictions	Non-English
Search dates	None

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

No economic evaluations in aHUS patients were identified through the systematic search.

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

The PRISMA diagram describing the results from the search is presented in Appendix 17.3. No economic evaluations in aHUS were identified through the search.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

No economic evaluations in aHUS patients were identified through the systematic search.

12 De novo cost-consequences analysis

Section 12 requires the sponsor to provide information on the de novo cost-consequences analysis.

The de novo cost-consequences analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

As required by NICE, Alexion presents analyses estimating the long-term benefits of treatment with eculizumab, and a cost comparison of use of eculizumab in atypical

Haemolytic Uraemic Syndrome (aHUS) patients vs. current standard of care (SOC). In undertaking these analyses, Alexion has sought to reflect the decision criteria specified by NICE in the document entitled *Interim Process and Methods of the Highly Specialised Technologies Programme*.[2] In the Interim Methods document, NICE explicitly recognises the unique nature of ultra-orphan diseases and the importance of deviating from the appraisal criteria used in conventional technology appraisals when evaluating drugs to treat ultra-orphan diseases:

> *"Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these vary rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their research and development investment because of the very small populations treated." (Page 8, Interim Methods document.)*

Specifically, the National Institute for Health and Care Excellence (NICE) has stipulated that decisions will not be based upon a single measure of cost-effectiveness; unlike in standard technology appraisals where incremental cost effectiveness ratios (ICERs) are judged against cost effectiveness thresholds to determine appraisal decisions. Instead, NICE has stated in the Interim Methods document that the Appraisal Committee will make its decision based upon six criteria:

- Nature of the condition (disease burden and unmet need);
- Impact of the new technology (clinical effectiveness and health benefit);
- Cost to the National Health Service (NHS) and Personal Social Services (PSS) (budget impact);
- Value for money (technical, productive and allocative efficiency);
- Impact beyond direct health benefits; and
- Impact of the technology on the delivery of the specialised service.

The information presented in this section of Alexion's submission relates to the "Value for Money" criterion. In the Interim Methods document, NICE describes the domains of relevance when assessing value for money:

- Technical efficiency (the incremental benefit of the new technology compared to current treatment);
- Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used); and
- Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning).

Therefore, in order to allow NICE to assess the "Value for Money" of eculizumab in the treatment for aHUS, Alexion presents the following analyses:

1) Incremental clinical benefit of eculizumab vs. SOC; and
2) Cost comparison of eculizumab vs. SOC.

[2] www.nice.org.uk/media/188/49/HST_combined_Interim_Process_and_Methods_FINAL_31_May_2013.pdf.

In keeping consistent with the NICE Interim Methods document for ultra-orphan diseases, no incremental cost effectiveness analysis has been undertaken

Given the requirement for a lifetime perspective and lack of comparative data against SOC prior to use of eculizumab, the above two analyses required modelling and extrapolation beyond the eculizumab clinical data. Such modelling in ultra-orphan diseases is subject to the same weaknesses inherent in cost utility analysis for such diseases, namely:

- Lack of data on the natural history of the disease, the cost of current care, and the burden of the disease on the patient, family and society;
- Small and heterogeneous patient populations;
- Varied care pathways with ill-defined standard of care;
- Clinical efficacy/effectiveness information based on small numbers of subjects in trials;
- Absence of information on quality of life in target population;
- Statistical issues in describing small samples; and
- Lack of established databases or algorithms from which to extrapolate trial data to life-time outcomes.

In addition to the above weaknesses, we further note that given eculizumab is the first and only European Medicines Agency (EMA)-approved therapy for the treatment of aHUS, the costs of treatment are additive to only some components of current SOC, including ESRF (plasma exchange/infusion are essentially eliminated with the use of eculizumab, and transplant may become unnecessary). As a result, “value for money” must be appropriately weighted to support positive clinical outcomes, not just lower expenditures.

As Alexion has discussed with NICE on numerous occasions, including during our scoping meeting and subsequent communications, caution should be used when attempting to interpret these analyses due to the relatively small body of aHUS disease information used to estimate patient outcomes over a lifetime. Such analyses are inherently prone to high levels of uncertainty and bias regardless of the modelling approach. For this reason, Alexion encourages NICE to consider the economic analyses presented in this section as auxiliary to the clinical data presented in Section C, which provides strong evidence of a large therapeutic effect for eculizumab based on well-conducted clinical trials in an ultra-rare disease state.

In addition, while there were notable delays due to change by government in the overall evaluation process, Alexion wishes to highlight the lack of time in which it has had to prepare the specific analyses and submission template now required by NICE. Alexion recognises that the new Highly Specialised Technologies Programme (HSTP) Interim Methods and submission template were created within a short period of time, but as a consequence, NICE was only able to discuss the exact nature of the economic analyses it desired during a call on July 31, 2013. This submission and related analyses have therefore been prepared in less than 6 weeks, which is extraordinary given that most similar analyses, both in the UK and other countries, typically take 6 to 12 months for completion.

12.1 Description of the de novo cost-consequences analysis

The cost consequences analysis compares an eculizumab treatment strategy with an SOC treatment strategy in a lifetime model for patients with aHUS initially presenting with signs of complement-mediated thrombotic microangiopathy (TMA).

Patients

12.1.1 What patient group(s) is (are) included in the cost-consequences analysis?

All patients in the analysis have aHUS and are initially presenting with signs of complement-mediated TMA.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-consequences analysis is different from the scope.

<u>Newly diagnosed people who have not received prior treatment:</u>

- plasma infusion and/or exchange

<u>Previously treated people with kidney impairment:</u>

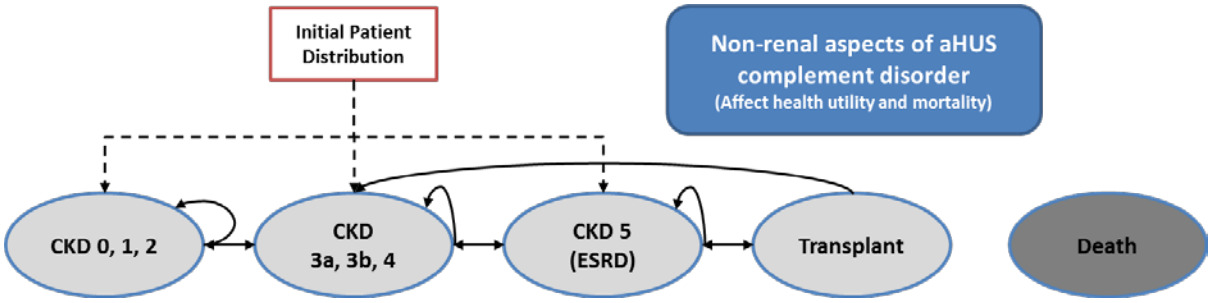
- kidney dialysis
- Kidney or kidney/liver transplantation

The cost-consequence analysis includes all of the above comparators except combined kidney/liver transplant because of the extreme rarity of this procedure due to the limited supply of solid organs, and the substantial near-term risk of mortality which is deemed too high by many physicians and patients.(Loirat 2008) After consulting with clinical experts, we are aware of only two cases of liver-kidney transplantation ever performed in the UK.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

Figure D1: aHUS Model Structure



The current model tracks patients through three chronic kidney disease (CKD) stages (CKD 0-2, CKD 3a-4, or CKD 5 [End-stage renal failure (ESRF)]), plus transplant and death. Patients may die from any state. Not modelled as separate health states due to data limitations are the non-renal effects of TMAs. TMAs may affect any of a number of different organ systems. However, owing to insufficient data for SOC, they are excluded. We implicitly assume their presence, using an excess mortality rate to reflect non-renal events that can be fatal, and the disutility associated with TMA, which is a justification for having different health utilities for the same health states for eculizumab and SOC-treated patients.

Each cycle spent in a Markov state is associated with a cost and an effect: in this model the units of benefit are life-years, years not in ESRF or death, and Quality-Adjusted Life-Years

(QALYs). As such, the model is a cost-utility model so that it can reflect the increase in quality of life seen in the clinical trials, along with the increase in length of life. At the end of the Markov process, average cumulative costs and effects are calculated for patients in a given treatment arm of the model.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model structure was reviewed by clinical experts, who found it appropriate. Both trials measured estimated glomerular filtration rate (eGFR), which is an important measure of kidney function, which is severely and chronically compromised in aHUS patients. eGFR is categorised into CKD stages, which form the primary structure of the model. Transplant is also commonly experienced by SOC-treated patients. TMA is not explicitly modeled, but is indirectly modeled by assuming the possibility of an excess mortality rate and differential health utilities between states for ongoing TMAs due to the underlying complement disorder.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Model assumptions are comprehensively detailed in later sections. Select assumptions include that we assume that CKD progression over time for eculizumab-treated patients can be derived from the C08-002 and C08-003 trials; we assume a Markov assumption when analysing these data.

- We assume that CKD progression over time for SOC-treated patients can be derived from the pre-treatment period of the C08-002 and C08-003 trials, based on the change in eGFR over time.
- We assume that the trajectory observed within the pre-treatment period persists. All patients in the ESRD state are assumed to receive dialysis. All are assumed not to receive plasma exchange, though experts did not rule this out (but thought it rare and could not provide a numeric estimate).
- We assume that after a successful transplant, patients have CKD 3a kidney function.
- We assume a transplant rate of 0% for eculizumab patients. There was one transplant observed in the C08-002 and C08-003 trials extension data (using the three year extension data.) The one event occurred at day 252 for one patient over 176.1 six-month intervals (32,051 days), yielding a six-month transplant rate of 0.57%. However, the one patient was waiting for a transplant prior to receiving eculizumab.
- We assume no excess risk of death for eculizumab patients; the model predicts higher mortality at year 3.5 based on background and renal death than has been observed in the trials.
- We assume that all aHUS patients who are in ESRD have a death rate consistent with that found in the UK Renal Registry for those in ESRD.
- We assume that SOC patients have an excess death rate based on TMA registry data, specifically Coppo et al (2010). The TMA registries select patients in a way more consistent with the eculizumab label than some recent aHUS registries like Noris et al (2010) and Fremeaux-Bacchi et al (2013).

12.1.6 Define what the model's health states are intended to capture.

The current model tracks patients through three CKD stages (CKD 0-2, CKD 3a-4, or CKD 5 [ESRF]), transplant, and death. TMA is not explicitly modeled, but is indirectly modeled by assuming the possibility of an excess mortality rate and differential health utilities between states for ongoing TMAs due to the underlying complement disorder.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table D2.

Table D2: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	The model has a 125-year time (i.e., 250 six-month cycles) horizon	The model has a 125-year time (i.e., 250 six-month cycles) horizon to capture lifetime costs and effects, and includes a background mortality rate so that approximately all persons exit before the final model cycle.	aHUS is a chronic lifetime condition, and the model has a 125-year time horizon to capture lifetime costs and effects
Discount rate	Discount of 1.5% per year for costs and benefits	A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.	Guide to the methods of technology appraisal 2013. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed September 8, 2013.
Perspective (NHS/PSS)	The analysis is taken from the perspective of the NHS	Drug administration costs, which will be borne by Alexion through homecare service for an estimated 80% of patients, are also included in the cost calculations. In addition, productivity benefits (calculated as the change in the percentage of patients who may participate in the workforce) are included in the model and can be included in the model output. Patient indirect costs are also reported.	None
Cycle length	6 months	The rationale for the six-month cycles is that results for eculizumab-treated patients in the Legendre et al. 2013 publication are presented at 6 and 12 months.	Legendre et al. 2013
Half-cycle correction	NA	The model employs a half-cycle correction for all costs and utilities in the first model cycle, except for the costs of eculizumab and plasma.	NA
NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-consequences analysis.

In this section, we explain how the results of the clinical evidence were incorporated into the model.

Primary Model Inputs

The model structure implies that several key efficacy inputs must be included. These are:

1. Eculizumab efficacy
    - Transitions between CKD and transplant states
    - Transitions to death

2. SOC efficacy
    - Transitions between CKD and transplant states
    - Transitions to death

We detail these parameters in the following sections.

Eculizumab Efficacy

Eculizumab efficacy data come from the C08-002 and 003 trials presented in Legendre et al., 2013, as well as from extension studies including up to 3.5 years of patient data. Legendre et al. reports outcomes in Table 2 of the publication. Extension phase data for study C08-002 and additional data for study C08-003 are also available.

Patient CKD stages were recorded at six month intervals from baseline. We estimated the Markov matrix for eculizumab used in the economic model. Transitional probabilities for eculizumab-treated patients involved health states for CKD 0, 1, 2, 3a, 3b, 4, and 5. Thus, the Markov matrix has seven CKD-based health states, as well as transplant and death. This change maximises sensitivity to changes in eGFR, and allows the results to be compared to Legendre et al. (After computing transitions and Markov traces, we roll up the seven states into three, per the structure diagram, including CKD 0-2, 3a-4, and 5.).

The first Markov matrix was calculated, using all observations of patients remaining in their CKD stage, or transitioning to a different CKD stage from baseline to week 26, per Figure D2. The vertical, far left column indicates the state from which a transition would occur; the horizontal header row indicates the state to which a transition would occur. Sample sizes appear in the column labelled “N”. The green shaded transitions indicate improvement, red shaded transitions indicate worsening, and white no change. As an example to facilitate interpretation of the table, per the row labelled “CKD 3a”, at baseline, there were three patients in CKD 3a (N=3). One-third of these patients transitioned to CKD 0, one-third to CKD 2, and the final third remained in CKD 3a at week 26.

[redacted]

A second Markov matrix was calculated for the change from week 26 to week 52, per Figure D3 below. The vertical, far left column indicates the state from which a transition would occur; the horizontal header row indicates the state to which a transition would occur. Green shaded transitions indicate improvement, red worsening, and white no change.

[redacted]

Matrices were also calculated from transitions from week 52 to week 78, week 78 to week 104, week 104 to week 130, week 130 to week 156, and week 156 to week 182. Missing patients were censored. A total of N=211 “transition” observations were observed, including observations covering approximately 176.1 six-month intervals. These matrices may be viewed on the sheet ‘ECU_trials_data’ in the electronic version of the model.

The seven transition matrices were combined into one memory-less matrix, based on an average of the seven prior matrices, weighted by the sample sizes of non-missing transitions. We assumed memory-less-ness, as this was the most parsimonious way to interpret the data. We would have preferred a time dependent matrix, but the given the sample size, this was prohibitive. We could have used a regression on eGFR and days in the treatment period to extrapolate a monotonically increasing eGFR and decreasing CKD state, but again, we thought that this may be unrealistic.

The matrix based on all transitions appears in Figure D4 below. Missing data were censored. We then used these probabilities as the basis for our six-month transitional probabilities in the revised model. The data and calculations used in the derivation of these

matrices appear in the attached Excel spreadsheet (highlighted light blue) in the electronic model (labelled “ECU_trial_data.”).

[redacted]

Transplant Rates for Eculizumab

The model also includes a transplant state. We assume a transplant rate of 0% for eculizumab patients. The one event occurred over 176.1 six-month intervals (32,051 days), yielding a six-month transplant rate of 0.57%. In the 002 and 003 trials, over 88.3 years, no patient received a transplant with one exception. One transplant was observed in a patient with long-term chronic dialysis and was a transplant candidate. This event was deemed not drug-related. Prior to study enrolment, the patient was already in stable ESRF (eGFR 5 ml/min/1.73m^2) with a serum creatinine of 893 µmol/L while dependent on chronic dialysis. While the patient was therefore already a transplant candidate, the patient would have been at high risk for loss of a transplanted kidney graft due to the underlying aHUS. However, after initiation of study drug (first dose of eculizumab on 9 November 2009), patient was then considered a candidate for transplant, and received the transplant on 14 June 2010 (day 217 of eculizumab treatment), after having completed the initial 26 week eculizumab treatment period. This patient continued to receive on-going eculizumab treatment during and following the successful kidney transplant.

Eculizumab: The transition from CKD 5/ESRF to Death

There are three reasons for which an eculizumab treated patient may die, including 1) being in ESRF and experiencing renal registry based death, 2) due to non-renal other causes of death related to aHUS (excess death), or 3) due to age- and gender-adjusted background death.

The renal registry based death rate (#2 above) is applied to all patients in CKD 5. We looked to the well-resourced registries assessing mortality in patients in ESRF and on dialysis. The UK Renal Registry reported in the 15th Annual Report (2012) in Chapter 5, Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011, "One year age adjusted survival for prevalent dialysis patients improved to 89.8% in the 2010 cohort from 89.1% in the 2009 cohort." We use the 2010 mortality to estimate the six-month rate from ESRF to death, which we use in the model as 5.1% per six months. We use this rate for SOC and for eculizumab-treated patients.

Eculizumab: Excess Mortality Rate

We assume an excess death rate, including for non-renal TMAs, to be 0% for eculizumab patients. There was one death observed in the C08-002 and C08-003 trials extension data

(using the three year extension data.) The one event occurred over 176.1 six-month intervals, yielding a six-month death rate of 0.57%. The death was determined not to be related to the study drug. The model assumes a death rate for eculizumab patients from ESRF (30% of patients start in ESRF) and from the background age- and gender-adjusted rate. The model predicts 4.9% mortality for eculizumab at year 3.5. Accordingly, we assume an excess death rate of 0% for eculizumab patients in the base case, and assume lower mortality from ESRF in a sensitivity analysis.

Of note, Kelly et al., 2011, followed 79 British patients with paroxysmal nocturnal haemoglobinuria (PNH) treated with eculizumab for 6.5 years and found statistically non-inferior mortality compared to the background rate, concluding: "Eculizumab dramatically alters the natural course of PNH, reducing symptoms and disease complications as well as improving survival to the extent that it is equivalent to that of the general population." More recent analysis of additional PNH data supports this assumption (Hillmen et al, 2013). Extrapolating from the PNH experience to aHUS should be done with caution, but given the aHUS data, the pathological process of complement disorders, and the therapeutic effect of eculizumab, and appropriately weighing the PNH experience, we assume that there is no excess risk of death for the eculizumab-treated patients in our base case. Of note, we test excess death rates for eculizumab in the sensitivity analysis.

<u>Eculizumab: Background Death</u>

Eculizumab background death is age-adjusted and derived from UK life tables.

Standard of Care (SOC) Arm Transitions

There are several SOC arm transitions which must be parameterised in the model, including:

1. The transitions between CKD states
2. The transition from CKD 5/ESRF to kidney transplant or death
3. The transition from kidney transplant to CKD5 (failure), death, or success (CKD 3a)
4. The excess death rate
5. Background death

The first transition was estimated based on data from the C08-0002 and C08-003 trials, and the other transitions come from the peer-reviewed literature and UK Renal Registry. In this section, we discuss how the first transition was estimated.

<u>SOC: Transitions between CKD States</u>

aHUS is a progressive and life threatening disease with 33% to 40% of patients reaching ESRF or death following the diagnosis. In two TMA registries (described in Coppo et al 2010 and Hovinga et al 2010, mortality of aHUS patients (TMA with ADAMTS13 > 10%) reached 13% (17.8 month mean follow up) and 32% (4.4 year median follow up), respectively. Further, the percentage of patients with reported acute renal failure was 21% and 54%, respectively, exemplifying the life-threatening and progressive nature of aHUS.

These databases are appropriate to measure the natural course of the disease since they recruited consecutively and non-selectively (not focused on renal failure alone) from intensive care units and departments of haematology, internal medicine and nephrology (Coppo et al). In the case of Hovinga, all TMA patients initiated PE, overcoming the inherent survivor bias due to the post hoc and/or retrospective nature of other aHUS specific registries. The Coppo and Hovinga datasets consist of adults with confirmed ADAMTS13

activity and no Shiga-Toxin producing enterohaemorrhagic *Escherichia coli* (STEC) infection, which is closely aligned to both the proposed clinical pathway of care and the eculizumab clinical trials population. Therefore, both the Coppo and Hovinga datasets present a realistic expectation of aHUS presentation and outcomes in adults.

In addition, the Coppo and Hovinga datasets present a large population at disease onset, and a broad definition of TMA, which reflects disease onset and does not limit TMA to voluntary patient enrolment by the treating physician or simply focused renal failure, as seen in other aHUS registries (Noris et al 2010, Fremeaux-Bacchi et al 2013). However, we recognised the lack of detailed progression or transition from CKD stage to ESRF, dialysis and finally mortality during SOC in both these publications since only one survival endpoint is reported at the median follow up.

In order to further support the published data and determine transitional probabilities, we use the pre-treatment period in the eculizumab clinical trial to determine the progression to ESRF/dialysis and mortality over time. In the published eculizumab trials (Legendre et al. 2013), eGFR, was measured for the pre-eculizumab treatment period. We used the eGFR data from the 002 and 003 clinical trials to estimate the relationship between time on SOC and the sample average effect on eGFR (as described below), which was then translated into six-month CKD transition probabilities.

The patients in the pre-treatment period in the trials received the complete array of SOC, including plasma exchange or infusion, dialysis, and/or transplantation as indicated, and therefore present a real world use of SOC in aHUS patients. The median number of SOC intervention events per day, including plasma exchange or infusion, dialysis, or both, was 0.88 and 0.23 in the two trials.(Legendre et al., 2013) There were 25 kidney transplants in 16 patients during the pre-treatment period.

Data and Methods - Analysis of relationship between eGFR and days using pre-treatment data

Legendre et al. 2013 detailed the outcomes of the 37 patients in 2 trials. Baseline demographic and clinical characteristics for the patients in the sample used in this analysis may be found in Table 1 in that paper.

The pre-treatment period was defined as the time from diagnosis to baseline in the trials.

The two trials combined contained 1,847 eGFR pre eculizumab treatment observations. The median interval between diagnosis and baseline was 186 days with a range of (965, 1) and interquartile range (IQR) of (334, 67). In the pre-treatment period, eGFR observations per patient average (min/max) 31.2 per patient (1/108). Note that prior to the screening period, these observations were collected retrospectively for enrolled patients.

The data structure of the retrospectively collected eGFR observations require that certain considerations be taken into account with regard to empirical analysis and interpretation. First, there are multiple observations per patient which, in many cases, were collected at irregular intervals. Second, these data are all survival-conditioned, meaning that for an eGFR observation to be included, it had to be from a patient who was alive with certainty at the beginning of the trial. Third, the pre-treatment data are left censored, as patients were diagnosed at irregular intervals prior to trial enrolment, meaning that the pre-treatment period is uneven between patients and the data forming an unbalanced panel. Note that the left hand censoring could be non-random, and correlated with severity of aHUS. How these empirical considerations were addressed is described below.

Methodologically, the goal is to determine the relationship between the change in eGFR to the number of days in the pre-treatment period, and map that relationship into the model in terms of likely transitions between CKD health states. Regression analysis—where the dependent variable is eGFR, and the key right-hand side variable is days to baseline—can estimate this relationship.

To begin with straight-forward estimation, we use an ordinary least-squares (OLS) model, specified as:

$$egfr_i = \alpha + \beta(days)_i + u_i \qquad (1)$$

where observation i of eGFR is $egfr_i$, (days) is days from diagnosis to baseline when $egfr_i$ was measured, α is the model intercept interpreted as the average eGFR for the sample at baseline, and u is the error term for observation i. All models were estimated in STATA v.13.

Ordinary least-squares (OLS) assumes that the error term for all observations is independently and identically distributed. However, the retrospectively collected observations are clustered within patients, likely violating this condition. The panel is also left-censored. To accommodate these issues, we use an unbalanced panel correction and estimate random effects and fixed effects models, which take advantage of the panel structure of the data to assess within or across patient variation in eGFR over time.

The random effects model estimates a patient-level random effect for each individual enrolled in the pre-treatment period, and uses this parameter to control for each patient's idiosyncratic eGFR trajectory. The effect estimated is an across patient sample effect. Observations use robust clustering; a generalised least squares (GLS) model estimated the association in the change in eGFR to the number of days in the pre-treatment period and the specification takes the form of:

$$egfr_{it} = \alpha + \beta(days)_{it} + u_i + e_{it} \qquad (2)$$

where patient i's observation of eGFR at time t is $egfr_{it}$, $(days)_{it}$ is days to baseline when $egfr_{it}$ was measured for patient i at time t, and u is idiosyncratic error term for patient i, and e_{it} is the remaining residual of observation i at time t. We also included a specification with a dummy variable controlling for the two trials as:

$$egfr_{it} = \alpha + \beta(days)_{it} + \beta(trial)_{it} + u_i + e_{it}. \qquad (3)$$

A fixed effects estimator was also used to assess the research question at hand. Fixed effects estimation involves using each patient as his or her own control to remove time invariant observed and unobserved variation that could be biasing the estimation. It estimates the effect within patients. The specification used was:

$$\ddot{egfr}_{it} = \beta(\ddot{days})_{it} + \ddot{u}_{it} \qquad (4)$$

where $\ddot{egfr}_{it} = egfr_{it} - \overline{egfr_i}$, or the egfr of patient i at time t minus the average for patient i ($\overline{egfr_i}$) over the entire pretreatment period. This value is demeaned, meaning that the average time invariant effects are controlled for each patient. Static patient characteristics, such as observables like patient race or unobservable characteristics like the patient's

(static) genetic propensity to suffer from aHUS, are removed as sources that could bias β, which is the change in eGFR per day on SOC. $Days_{it}$ and u_{it} are similarly demeaned.

Results-Analysis of relationship between eGFR and days using pre-treatment data

The results appear in Table D3 below. All coefficients are negative, indicating that as time passes, the sample average kidney function diminishes for patients treated with SOC. The OLS estimate is -0.024, meaning that for each day on SOC, eGFR declines by 0.024 points (ml/min/1.73 m^2) per day. The random effects coefficient is largest; controlling for trial does not alter the expected decline in kidney function. The fixed effects coefficient is similarly sized, and was chosen for the model base case owing to its ability to control for within patient effects.

Table D3: eGFR decline per day in the pre-treatment period in patients receiving SOC

Model & Specification	Coefficient on days (β)	Std. Error	p value	Constant (α)
OLS regression				
(1)	-0.024	0.002	0.000	22.505
Random-effects GLS regression				
(2)	-0.031	0.006	0.000	24.302
(3)	-0.031	0.006	0.000	28.095
Fixed-effects regression				
(4)	-0.030	0.003	0.000	20.884

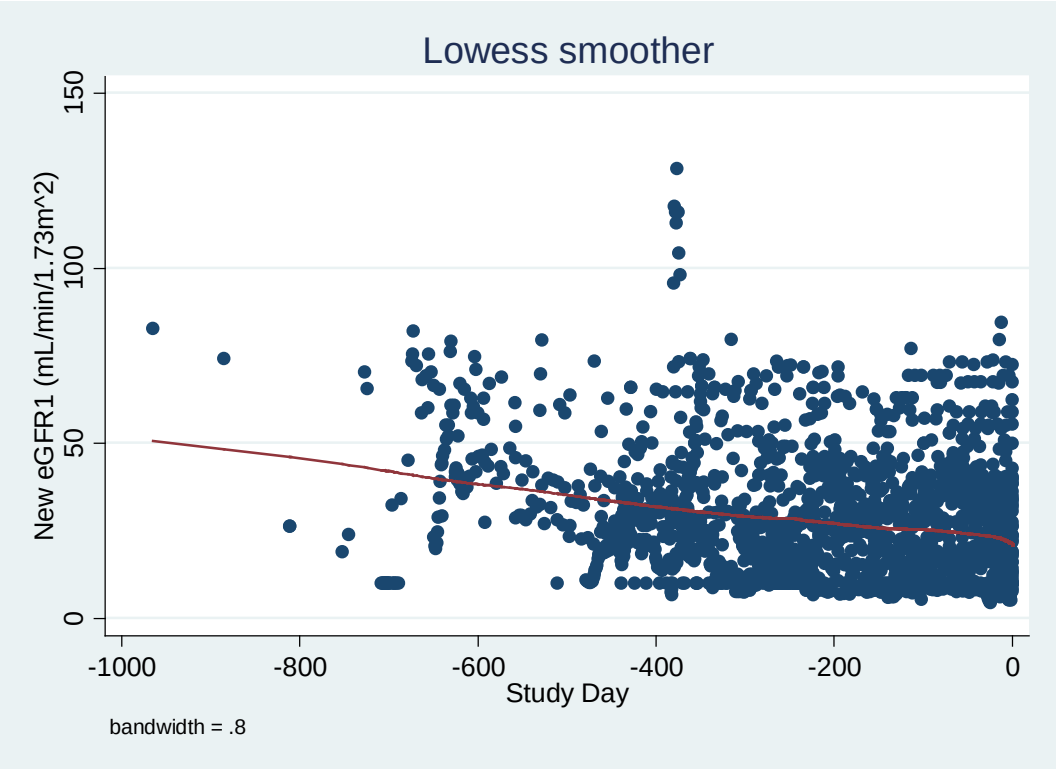
Testing the linearity assumption: Is it reasonable to assume SOC treated patients would continue to get worse?

Given the unbalanced nature of the panel, it is reasonable to question whether the relationship between eGFR and days is linear. For example, it could be that patient kidney function deteriorated closer to the beginning of the trial. If we fitted a linear model and assumed a linear effect into the future, but such an effect was really confined to one part of the data (i.e., the three months before baseline), we would gravely misestimate the long-run trajectory of kidney function in SOC-treated patients. The direction of the bias is unpredictable, but we address this issue with a locally weighted scatterplot smoothing (LOWESS) regression.

LOWESS is a non-parametric regression method that combines multiple regression models in a k-nearest-neighbor-based meta-model. LOWESS repeatedly fits simple models to localised subsets of the data to build up a function that describes the deterministic part of the variation in the data, point by point. In fact, one of the chief attractions of this method is that the data analyst is not required to specify a global function of any form to fit a model to the data, only to fit segments of the data.

The results of the LOWESS regression are presented in Figure D5 (the default bandwidth of 0.8 was used in the smoothing function). By visual inspection, we judge the line to be reasonably straight, indicating that the effect of eGFR on days is linear, and that it is reasonable to assume that the effect would continue were patients to continue on SOC.

Figure D5: LOWESS smoothing regression effects on eGFR and days in the pre-treatment period.



Limitations-Analysis of relationship between eGFR and days using pre-treatment data

This analysis likely understates the decline in kidney function for at least four reasons. First, to be in the pre-treatment group, one had to enrol in the trial (and be alive). That is, all patient observations are conditioned on the patient surviving to the beginning of the trial. The model does not include aHUS patients who died shortly after diagnosis (Noris et al., Fremeaux-Bacchi et al.). The effect of excluding patients who experience early mortality (and who would be indicated for eculizumab) likely leads to an underestimation of the magnitude of change in eGFR per day, as the estimate used in this model only reflects kidney decline in those who survived. This could be a major source of bias in favour of SOC.

Second, eGFR is bounded at 0. The linear models used assume that the dependent variable, eGFR, is linear and continuous, and not bounded at zero. They could be misestimating the effect.

Third, most patients on dialysis do not have eGFR measurements. In these cases, measures were imputed to be “10”, so there is a higher “floor” or minimum value for many patients in ESRF.

Fourth, local labs measured eGFR in the pre-treatment period, while specialty trial labs measured it in the study period. Specialty trial labs would minimise measurement error in eGFR measurements, while local labs measures would be expected to have more such measurement error. Such mis-measurement, assuming it is random, would attenuate the coefficient relating eGFR change to days to zero, again biasing the estimate to be lower than the real rate of decline.

Parameterising the model with CKD transition likelihood for SOC-treated patients

The fixed effect coefficient estimate is -0.030 in the prior table indicates, meaning that for each day on SOC, eGFR declines by 0.030 points (ml/min/1.73 m^2) per day, which translates to a -5.498 decrease per 182 days (six months). Assuming patients are uniformly distributed over the a CKD interval, which is 15 eGFR points, this translates to: |-5.498|/15 = 0.367, or a 36.7 percent chance of declining one CKD stage every sixth months when treated with plasma exchange, dialysis, and/or kidney transplant. This compares to a six month increase (improvement) in CKD of at least 1 stage in trial 1 and 2 of 59% and 35%, respectively, in Legendre et al.

<u>SOC: Transition from CKD 5/ESRF to Death</u>

As stated above, while there are reports of overall mortality in aHUS patients, there are limitations to how the data are reported. Specifically no data identified assesses the progressive mortality rate for aHUS patients in CKD 5/ESRF or dialysis in a well-controlled study. We looked to the well-resourced registries assessing mortality in patients in ESRF and on dialysis. The UK Renal Registry reported in the 15th Annual Report (2012) in Chapter 5, Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011, "One year age adjusted survival for prevalent dialysis patients improved to 89.8% in the 2010 cohort from 89.1% in the 2009 cohort." We use the 2010 mortality to estimate the six-month rate from ESRF to death, which we use in the model as 5.1% per six months. We use this rate for SOC and eculizumab-treated patients.

Of note, patients do not die from ESRF, *per se*. The causes of death on dialysis is numerous and includes systemic complications such as acute myocardial infarction, cardiomyopathy, cardiac arrhythmia, cardiac arrest, congestive heart failure, pulmonary edaema, cerebrovascular disease, GI haemorrhage, pulmonary infection, viral infection, withdrawal form dialysis.(United States Renal Data System (USRDS) 2012, Section H Mortality tables). In the UK, patients die from similar causes, including cardiac disease (27%), infection (17%), treatment withdrawal (15%), among other causes while in ESRF, according to Table 5.20 in the 15th Annual Report (2012).

Causes of death while on dialysis overlap with the systemic complications due to complement mediated TMA in aHUS patients. Perkins et al (2006) reported that the incidence of TMA was the highest in the first year of dialysis among patients with renal failure due to HUS, occurring in 11.3% patients at one year and in approximately 4.5% patients annually thereafter while the incidence of TMA in patients on dialysis without HUS is a consistent 0.3% annually. This suggests 29% of patients will have a TMA during dialysis at 5 years in HUS patients. These effects are assumed to inform the disease process in aHUS and to be already incorporated in the CKD and ESRF states of the model.

<u>SOC: Transplant rates, Transition from CKD 5 to Kidney Transplant</u>

The model also includes a transplant state. The transplant rate for SOC is based on an analysis of C08-002 and C08-003 pre-treatment data. For the N=37 patients in the trials, there were 25 transplants in 16 patients over the pre-treatment study time period (71.6 six-month increments). This equates to a transplant rate of 34.9% per six months for eculizumab patients. We assume that this transition is only possible for patients in the CKD5 state.

<u>SOC: Kidney Transplant Outcomes—Transitions from Kidney Transplant to CKD5 (failure), Death, or Success (CKD 3a)</u>

Kidney transplantation does not rectify the continued and uncontrolled complement activation leading to progressive disease and premature mortality in aHUS patients. Among patients with aHUS who undergo kidney transplantation without eculizumab "graft failure is reported in 60 to 90% of patients within 1 year", (Legendre et al 2013; Zuber 2011; Le Quintrec 2013; Noris et al 2010). Thus, we assume that 75% (mid-point of 60 and 90%) of patients who undergo kidney transplant have the organ fail within six-months. Following transplantation, renal function is not expected to perform like a perfectly health kidney, and the overall bodily renal function would not be CKD 0. The health and function of the transplanted kidney rely on the donor, efficacy of and compliance with the post-transplant immunosuppressive regimen, delayed graft function, and other factors. In one large study evaluating 4,488 graft recipients with no aHUS, the mean eGFR was 51.2 ml/min/1.73m^2 at 3 months following transplantation and 60% of patients had CKD stage 3 at 12 months following transplantation (27% at stage 2 and 10% at stage 4).(Marcen et al NDT 2010) Therefore for patients that did not lose their graft after one year due to aHUS we transitioned to CKD 3a.

The mortality rate in the transplant state, that is the transition from transplant to death, is assumed to the same as the mortality rate in the CKD 5 (ESRF) state: 5.1% per six months, based on expert opinion. UK clinical experts indicated that it should be at least the same, and perhaps a “bit higher”. The remainder (65%) of the failures stay in CKD 5.

<u>SOC: The Excess Death Rate</u>

As already described, the model includes transitions for patients through CKD stages to ESRF, and then to death. aHUS, however, is not only a renal disease, but is a complement disorder which has systemic effects, leading to neurological, cardiovascular, and gastrointestinal life-threatening complications. Additional excess mortality is possible for SOC-treated patients.

An aHUS excess non-renal mortality rate was based on the N=54 cohort of patients with aHUS (defined as detectable a disintegrin and metalloproteinase with thrombospondin-1 motifs [13th member of the family] (ADAMTS13) activity of 10% or more with TMA, see Table 3) in Coppo et al. (2010), the results of which indicated that 13% (7/54) of patients had died after a mean follow-up of 17.8 months. In the SOC arm of the model, when no excess death is applied to SOC-treated patients (they only die from CKD to ESRF to death progression and the background rate), mortality at 18 months (1.5 cycles) is 6.1%. The difference in the mortality observed in Coppo et al. versus predicted mortality at 18 months was 6.9%. A non-renal excess death rate, considering the renal and background death rates, was calculated to be 4.0% per six months using the solver function in Microsoft Excel, so that mortality after 18 months in the model (3 model cycles) years was equal to the 13% observed in Coppo et al (2010).

Alternatively, a second aHUS excess non-renal mortality rate was based on the N=201 cohort of patients with ADAMTS13 activity of 10% or more in Hovinga et al. (2010), the results of which indicated that 32% of patients had died after median follow up of 4.4 years (see Figure 4). A non-renal excess death rate, considering the renal and background death rates, was calculated to be 2.9% per six months using the solver function in Microsoft Excel, so that mortality after 4.5 years was equal to the 32% observed in Hovinga et al 2010. We use Coppo et al (2010) data in the base case to make this calculation for comparison purposes.

<u>SOC: Background Death</u>

SOC background death is age-adjusted and derived from UK life tables.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Costs and benefits were extrapolated into the future. For eculizumab, the Markov process (see prior section) parameterised up to 3.5 years of C08-002 and C08-003 data (i.e., the three-year extension period) is assumed to continue into the future. For SOC, renal function is assumed to continue to decline linearly. The LOWESS regression assessed (see prior section) whether the functional form of the eGFR and days relationship was linear within the pre-treatment period, which average almost one year per patient. We assumed this process would have continued had they not received eculizumab.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The CKD state transitions are parameterised based on an intermediate measure, eGFR (see prior section). Data were used from the trials. In the validation section at the end of Section 12, we compare how our model's joint endpoint of ESRF and death compares with others in the literature.

12.2.4 Were adverse events included in the cost-consequences analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event (AE).

Eculizumab is generally very well tolerated. Adverse reactions were mostly mild to moderate in severity. The most commonly reported AEs from the two main eculizumab trials were headache, dizziness, nausea, and pyrexia, each occurring in 5% or more patients. Although almost all patients reported AEs in the aHUS studies, few were considered drug-related by the investigators.

In the two prospective aHUS studies, there was only one AE which led to treatment discontinuation, and this AE was deemed unrelated to study drug. The AE profile with eculizumab treatment of aHUS patients is therefore consistent with the safety profile with eculizumab previously reported in PNH patients.

Importantly, the AEs of SOC <u>have never been</u> evaluated in similar research. There has never been a clinical trial measuring the AE rate (or other outcomes) of plasma exchange, plasma infusion, dialysis or kidney transplant in patients with aHUS. The pre-treatment period of Legendre et al. was retrospectively analysed, so AEs were not recorded in the manner they would be in C08-002 or C08-003. Frequent and severe AEs have been documented for PE/PI in patients receiving this for all possible indications, as detailed elsewhere in the submission.

Since the AE profile is generally mild for eculizumab, and there is no specific trials source for SOC, the model does not include any health or cost implications for treatment-related AEs.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical experts in the United Kingdom (UK) in aHUS were consulted as part of the preparation of the eculizumab NICE submission to help address the significant lack of available evidence concerning the manifestation of the disease. Specifically, experts were consulted with the following objectives:

- To validate the disease burden, standard of care, and treatment pathway in aHUS;
- To provide context around the eculizumab clinical trial data;
- To support the structure of the eculizumab incremental survival model; and
- To provide feedback on model parameters.

Participants

Clinical experts were chosen to be invited to participate in the review based upon the following criteria (not all criteria had to be met):

- Practicing at a tertiary referral centre for aHUS in the UK;
- Author of published articles concerning aHUS; and/or
- Experience using eculizumab in aHUS patients.

Alexion approached five experts, all of whom agreed to participate:

- Professor Tim Goodship, Professor of Renal Medicine, University of Newcastle upon Tyne
- Dr Daniel Gale, Consultant Nephrologist, Royal Free Hospital;
- Dr Rodney Gilbert, Consultant Paediatric Nephrology, University Hospital of Southampton;
- Dr David Kavanagh, Consultant Nephrologist, Newcastle Hospitals; and
- Prof Neil Sheerin, Professor of Nephrology, Newcastle Hospitals.

Involvement

The five experts participated in telephone interviews lasting 60 to 90 minutes and answered a series of questions listed in Appendix 17.6. Delphi techniques and other iterative data collation techniques were not employed. No pre-reading or background information was provided to experts before or during the interviews.

12.2.6 Summarise all the variables included in the cost-consequences analysis. Provide cross-references to other parts of the submission.

Table D4: Summary of variables applied in the cost-consequences model

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
Age at baseline, average	28	None	No	Prospective trials, C08-002 and C08-003, at baseline (median and unreported mean)

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
Baseline CKD distribution			Yes, C08-002 and 003 patients were bootstrapped with replacement, which varied the baseline distribution	Prospective trials, C08-002 and C08-003, at baseline
CKD 2	0.054	N=37		
CKD 3a	0.081	N=37		
CKD 3b	0.270	N=37		
CKD 4	0.297	N=37		
CKD 5	0.297	N=37		
Background mortality (6 month)	Varies by age	NA	No	Interim Life Tables for England, 2009-2011, Office of National Statistics
Patient weight intervals			No	Based on Alexion experience and forecast in the UK
Paediatric patients weighing 5-10kg	0.1	NA		
Paediatric patients weighing 10 - < 20kg	0.1	NA		
Paediatric patients weighing 20 - < 30kg	0.1	NA		
Paediatric patients weighing 30 - < 40kg	0.1	NA		
Adult dosing weight (> 40kg)	0.6			
Eculizumab efficacy, progression through CKD stages	See Markov Matrix	Bootstrap with replacement, non-parametric variation	Yes, C08-002 and C08-003 patients were bootstrapped with replacement	Prospective trials, C08-002 and C08-003; See Markov Ecu

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
SOC excess death (except from transplant/ESRF), 6-month transitional probability	0.04	N=54	Yes, beta distribution, N=54, 13% mortality at 17.8 months	Coppo et al. 2010 (based on 13% mortality at 17.8 months)
SOC likelihood of a 15 point EGFR drop, 6-month transitional probability	0.367	Standard error (SE) in regression	Yes, normal distribution, mean= coefficient, Standard Deviation (SD)=SE	Data analysis C08-002 and C08-003 of pretreatment period
SOC likelihood of a 30 point EGFR drop, 6-month transitional probability	0	NA	No	Data analysis C08-002 and C08-003 of pretreatment period
SOC likelihood of a kidney transplant conditional in being in ESRF	0.349	N=37	Yes, beta distribution, N=37, 25 event per 352*37 days	Pretreatment period, C08-002 and C08-003. In the pretreatment period, there were (352*37) days of observation time. 25 transplants were recorded in 16 patients.
SOC transplant success transitional probability	0.25	NA	Yes, uniform distribution between 40% and 10%	Midpoint of "Graft failure is reported in 60 to 90% of patients within 1 year", (Legendre et al 2013; Zuber, 2011; Le Quintrec 2013; Noris et al 2010)
SOC transplant mortality transitional probability	0.052	NA	Yes, normal distribution, 95% confidence interval (CI): 89.3,90.2	Expert opinion consensus: "a bit higher than ESRF rate"
ESRF excess mortality transitional probability	0.052	95% CI: 89.3,90.2	Yes, normal distribution, 95% CI: 89.3,90.2	UK Renal Registry 15th Annual Report (2012): Chapter 5 Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011: national and centre-specific analyses. "One year age adjusted survival for prevalent dialysis patients [was] 89.8% in the 2010 cohort"
Health State Costs				
CKD 0, 1, 2 care costs	£480	SD=mean	Yes, gamma, assume SD=mean	See section 12.3.1

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
CKD 3, 4 care costs	£485.5	SD=mean	Yes, gamma, assume SD=mean	See section 12.3.1
ESRF	£12,141	SD=mean	Yes, gamma, assume SD=mean	See section 12.3.1
Transplant cost	£18,792	SD=mean	Yes, gamma, assume SD=mean	See section 12.3.1
Transplant success (kidney function restored to CKD 3a), ongoing	£3,320.5	SD=mean	Yes, gamma, assume SD=mean	See section 12.3.1
Cycles of post transplant care	1		No	Assumption
Treatment Costs				
Price of biologic eculizumab per vial	£3,150	None	No	See section 12.3.1
Induction doses (1/2 year)	42.9	None	No	See section 12.3.1
Maintenance doses (1/2 year)	39.8	None	No	See section 12.3.1
Biologic cost-induction period (first six months)	£135,135	None	No	See section 12.3.1. Also included is for £30 meningococcal vaccine and £512 for eculizumab administration costs
Biologic cost-maintenance period (subs. six months)	£125,370	None	No	See section 12.3.1. Also included is £512 for administration costs
SOC therapy cost (PLEX), adult	£15,574	None	No	See section 12.3.1
SOC therapy cost (PLEX), child	£22,620	None	No	See section 12.3.1
Discount rate, costs	0.015	NA	No	Guide to the methods of technology appraisal 2013. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed 9/8/2013

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
Health utility increase from Ecu	0.208	N=37	Yes, based on means and SDs reported in Legendre et al. for each trial	Legendre et al. (2013), at week 64
aHUS (SOC) Health Utility (annual increments)				
CKD 0, 1, 2	0.792	0.22	No, Ecu health utility (HU) minus HU increase from Ecu equal aHUS (SOC) HU	prospective trials, C08-002 and C08-003, at baseline
CKD 3, 4	0.662	0.345	No, Ecu health utility (HU) minus HU increase from Ecu equal aHUS (SOC) HU	prospective trials, C08-002 and C08-003, at baseline
ESRF	0.659	0.343	No, Ecu health utility (HU) minus HU increase from Ecu equal aHUS (SOC) HU	prospective trials, C08-002 and C08-003, at baseline
Eculizumab Health Utility (annual increments)				
ecu + CKD 0, 1, 2	1	0	Yes, beta	prospective trials, C08-002 and C08-003, at week 52
ecu + CKD 3, 4	0.870	0.189	Yes, beta	prospective trials, C08-002 and C08-003, at week 52
ecu + ESRF	0.867	0.18	Yes, beta	prospective trials, C08-002 and C08-003, at week 52
Transplant	0.662	0.345	No, Ecu health utility (HU) minus HU increase from Ecu equal aHUS	Assumed to be same as SOC CKD 3a (Marcen et al NDT 2010)

Variable	Mean	Sample size, Std Dev	Varied in probabilistic sensitivity analysis (PSA) and distribution assumed	Source
Discount rate, health utility	0.015	NA	No	Guide to the methods of technology appraisal 2013. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed 9/8/2013

12.3 Resource identification, measurement and valuation

NHS Costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is no specific reference cost for patient with aHUS. Standard care of aHUS patient includes plasma therapy, dialysis in ESRF patients and kidney transplantation, which are coded and available as reference costs for 2011/2012. It should be noted that because these procedures are not aHUS specific, the reference cost data may not reflect the full cost of the procedures for aHUS patients, who are likely to represent particularly complicated cases.

Plasma therapy, Healthcare Resource Groups (HRG) SA13A-SA16Z, reference costs are separated for adult and child patients for single session and also provided for inpatient plasma therapy with duration over 2 days. For plasma therapy there are available 2013/14 year PbR tariffs for outpatient and combined procedures.

Dialysis reference costs, HRG LD01A-LD13A, are separated by mode of dialysis (location of care and form of access), and also separated for adults, children and patients with blood borne virus. No 2013/14 PbR tariffs are available for dialysis.

Kidney transplant reference costs, HRG LA01A- LA03B, vary depending on the type of donor. No 2013/14 PbR tariffs are available for transplant.

The following section describes how reference costs and payment by results tariffs were applied in our model.

<u>Dialysis</u>

All patients in the ESRF state are assumed to receive dialysis; the cost of dialysis is taken into account in addition to ESRF care cost. The model uses the cost of dialysis (added to the costs of ESRF care) based upon a weighted average reference cost for NHS 2011/2012 of HRG LD01A, LD01B, LD02A, LD02B, LD03A, LD04A, LD04B, LD05A, LD05B, LD06A, LD06B, LD07A, LD08A, LD09A, LD09B, LD10A, LD10B, LD11A, LD11B, LD12A, LD12B, LD13A. The weighted unit cost was based upon the level of activity for each form of dialysis.

Yearly cost is calculated assuming a haemodialysis frequency of three times per week and daily for peritoneal dialysis (the same assumption is used in the costing report for the NICE Clinical Guideline 125 “Kidney disease: peritoneal dialysis” issued July 2011. The weighted

average cost of dialysis in adult patients (19 year old and over) is £23,300 per year and £38,945 for patients 18 years or younger. We use adult costs in the base case analysis.

The highest and lowest reference costs were examined from across the HRG codes. The difference in high and low costs was about 10 percent; in sensitivity analysis, we used +/- 50%.

Plasma Therapy (plasma exchange/plasma infusion)

In addition to the costs of CKD care, all standard of care patient costs include plasma therapy, with the exception of when the patient is in ESRF. Plasma therapy costs used in the model are based upon the reference cost for NHS 2011/2012.

Guidelines suggest that plasma exchange is initially carried out daily for the first five days after diagnosis, followed by five times a week for the following two weeks and three times a week for next two weeks.(Ariceta et al. 2009) In the month immediately following diagnosis, it is therefore recommended that the patient undergoes 21 plasma exchange procedures, although this may be adjusted depending on the patient response.(Taylor et al. 2009)

No clinical guidelines exist that address the long-term frequency of plasma exchange/infusion. In rare cases, plasma exchange/infusion is stopped entirely but it is far more common that prophylactic plasma exchange or infusion will be required as the patient becomes plasma dependent.(Kim et al. 2011)

In the model plasma exchange frequency was therefore assumed to be once per week on an on-going basis. This assumption was supported by expert opinion.

Annual plasma costs were based upon the upper quartile unit cost for day cases, using the HRG code SA13A for adults (£599 per session) and SA13B for children (£870 per session). This produces an annual cost of £31,142 for adults and £45,217 for children. The upper quartile costs were chosen because patients with aHUS are likely to represent the more expensive component of the case mix included in these reference costs. There are two reasons for this:

1. The need for larger quantities of plasma to be infused for aHUS patients compared with patients being treated with plasma exchange for other diseases. Current aHUS paediatric treatment guidelines recommend exchanging 1.5 times the patient's body weight expected plasma volume (equivalent to 60–75 mL/kg body weight).(Ariceta et al. 2009) This compares with 40–55 mL/kg used in Guillian-Barre syndrome.(Raphael et al. 2008) Feedback from UK aHUS experts suggests that the volume required for adults can also be greater, with patients requiring 3 to 4 litres per session.

2. Unlike plasma exchange in other conditions, patients with aHUS require replacement with whole plasma (Octaplas®).(Ariceta et al. 2009) This was confirmed by expert feedback. In contrast, transfusion guidelines for plasma exchange for other non-aHUS diseases (e.g. Guillain-Barre syndrome) from the UK Blood Services (McClelland D. 4th Edition) recommend replacement with albumin and saline, which is associated with a lower cost per unit.

The sensitivity analysis therefore uses a "high scenario" value of £70,958 for adults and £41,392 for patients 18 years old and younger. This value represents just the cost of plasma for a session of plasma exchange assuming that 60ml/kg of Octaplas is infused per session for adult patients with an average weight of 60kg and children with an average weight of 35kg. The model uses weekly frequency of plasma exchange and a unit price for Octaplas

of £75.81. This cost does not include any of the other costs (staff, disposables, machines, bedspace) involved in providing plasma exchange, and thus is still a conservative estimate.

The "low scenario" value of plasma therapy assumes costs that are 50% of the base case.

Kidney transplantation

Kidney transplant costs are derived from NHS reference costs 2011/2012 using the following HRG codes: LA01A LA01B LA02A LA02B LA03A LA03B. Average costs for adults and children were calculated using unit costs weighted according to activity levels. For adults (patients 19 years old and over) the cost is £18,792 and £24,626 for children (age 18 and less).

For the lowest and for the highest cost in sensitivity analysis the model assumes the lowest and the highest 2011/2012 year reference cost of kidney transplant, respectively.

Annual Transplant Maintenance Cost

No reference costs or PBR tariffs were available to estimate the on-going annual cost for patients after transplantation (e.g immunosuppressive therapy). Therefore these costs were obtained from the 2006 NICE Technology Appraisal N85 "Immunosuppressive therapy for renal transplantation in adults" and inflated to 2012 cost using the Personal Social Services Research Unit (PSSRU) NHS cost inflator. Three different 10 year post-transplant cost ranges were estimated in the appraisal for each of the three immunosuppression drugs: £48,736-£76,144, £23,204-£23,803, and £51,005-£38,527. An average annual cost of £6,641 was used in the base case with the lowest value (£3,102) and highest value (£10,180) used in sensitivity analysis.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review was undertaken to support the creation of the model described in Section 12. The literature review was specific to aHUS. Given the very small body of published evidence in this disease, a broad search was undertaken to obtain the following information:

- Information on resource use and costs in aHUS
- Economic studies in aHUS
- Quality of life data in aHUS

The search criteria, search results and extraction tables are included in Appendix 17.4.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[3].

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

United Kingdom experts in aHUS were consulted as part of the preparation of the eculizumab NICE submission to help address the significant lack of available evidence concerning the manifestation of aHUS. Specifically, experts were consulted with the following objectives:

- Understanding the disease burden, standard of care, and treatment pathway in aHUS
- Providing context to the eculizumab clinical trial data
- Supporting the structure of the eculizumab incremental survival model
- Providing feedback on model parameters

Participants

Clinical experts were chosen to be invited to participate in the review based upon the following criteria (not all criteria had to be met):

- Practicising at a tertiary referral centre for aHUS in the UK
- Author of published articles concerning aHUS
- Experience of using eculizumab in aHUS patients

Alexion approached five experts of which the following four individuals agreed to participate:

- Dr. Daniel Gale, Consultant Nephrologist, Royal Free Hospital;
- Dr. Rodney Gilbert, Consultant Paediatric Nephrology, University Hospital of Southampton;
- Dr. David Kavanagh, Consultant Nephrologist, Newcastle Hospitals; and
- Prof. Neil Sheerin, Professor of Nephrology, Newcastle Hospitals.

Involvement

The four experts participated in telephone interviews lasting 60 to 90 minutes and answered a series of questions listed in Appendix 17.6. Delphi techniques and other iterative data collation techniques were not employed. No pre-reading or background information was provided to experts before or during the interviews.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

One 300 mg vial of eculizumab is currently priced at £3,150 (excluding VAT).

12.3.5 If the list price is not used in the de novo cost-consequences model, provide the alternative price and a justification.

The list price is used in the model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequences model. Please consider all significant costs associated with treatment that may be of interest to commissioners.

One 300 mg vial of eculizumab is currently priced at £3,150 (excluding VAT). The dosing schedule for patients over 40kg for the initial (induction) phase is 900 mg weekly for four weeks and the dosing schedule for the maintenance phase is 1200 mg at Week 5 and then 1200 mg every two weeks thereafter. Paediatric patients with body weight ≥ 40kg are treated with the adult dosing recommendations. In paediatric PNH and aHUS patients with body weight below 40 kg, the Soliris dosing regimen consists of the dosing schedule in Table D5 below.

Table D5: Eculizumab Dosing Schedule

Patient Body Weight	Initial Phase	Maintenance Phase
30 to <40 kg	600 mg weekly x 2	900 mg at week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly x 2	600 mg at week 3; then 600 mg every 2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg at week 2; then 300 mg every 3 weeks

Eculizumab costs over a six-month period appear for the five different dosing groups below, which are determined by patient weight (Table D6).

Table D6: Eculizumab costs for weight groups

Weight Cohort	Induction vials	Maintenance vials	Induction cost	Maintenance cost
5 - <10kg	10	8	£31,500	£25,200
10 - <20kg	15	13	£47,250	£40,950
20 - <30kg	28	26	£88,200	£81,900
30 - <40kg	40	39	£126,000	£122,850
> = 40kg	56	52	£176,400	£163,800

We assume a distribution the dosing schedule based on the weight of the cohort at baseline per the Table D7 below. Within each dosing category, we assume an age at baseline (Column 3) which corresponds with the midpoint of the weight range for a given cohort using UK Health Survey for England 2011 weight data.(Craig R, Mindell J (eds) (2012) Health Survey for England 2011, London: The Information Centre. http://www.ucl.ac.uk/hssrg/studies/hse, Last accessed 9/7/2013) For example, the midpoint of the fourth cohort is 35 kg, which corresponds to the median weight of a (gender-adjusted) 9.5 year old. We then age each of the five weight cohorts in the model, assuming that their weight follows a schedule by their age, based on the median gender-adjusted weight by age using Health Survey for England weight by age data.(Craig R, Mindell J, 2012)

As the cohorts age and their weight increases based on the UK Health Survey for England data, and we modify the maintenance doses consumed each model cycle as they age. For example, the third cohort is 25 kg and 6.5 years old at baseline. In about 2 years (4 model cycles), they are 8.5 years old, and weight about 30 kg; they move from the third to the fourth maintenance dosing schedule at this point in the model. In 8 cycles, they are 10.5 years old, and are 40 kg, and switch to the adult dosing schedule.

Table D7: Patient weight by age

Weight Cohort	Distribution assumed at baseline	Age at baseline	Weight at baseline
5 - <10 kg	[redacted]	0.5	7.5 kg

Weight Cohort	Distribution assumed at baseline	Age at baseline	Weight at baseline
10 - <20 kg	[redacted]	2.5	15 kg
20 - <30 kg	[redacted]	6.5	25 kg
30 - <40 kg	[redacted]	9.5	35 kg
> = 40 kg	[redacted]	> 12	> 40 kg

The model uses the same comparator as in clinical studies, SOC. The main component of standard of care is plasma exchange. Calculations for the cost of plasma therapy vary for paediatric and adult patients and are based on reference cost and were described in Section 12.3.1. We assume that paediatric patients are those under 40 kg. Using the same assumptions about starting age and weight, and weight increase with aging, we modify the distribution of the paediatric/adult plasma cost over time (Table D8, Table D9).

Table D8: Costs per treatment/patient associated with Eculizumab for adult patient in the cost-consequences model

Items	Value	Source
Price of the technology per treatment/patient	£176,400 for induction for first 6 months and £163,800 per 6 months in maintenance for adults. For paediatric induction and maintenance dosing, we calculated the following costs per six months	Soliris SmPC
Administration cost	Administration of eculizumab (normally at home) will be funded by Alexion as part of the aHUS homecare initiative. Eighty percent of patients are assumed to be enrolled in this program. At an estimated cost of £300 per patient per month this would total £1,800 in a six-month period. Since these costs are being paid by Alexion, they are not included in the baseline figures for the model. Those patients (20%) who are not in this program will receive about 13 administrations per month, costing about £197 per administration. There is also a £30 cost for a meningococcal vaccine at induction.	Infusion costs are based on £197, per "Deliver simple parenteral chemotherapy first attendance (Currency Code SB12Z)." We assume 13 administrations per six months. We assume the cost of Menveo (meningococcal A, C, W135 and Y conjugate vaccine) at £30.00 per the British National Formulary, August 2013
Training cost	None	N/A
Other costs (monitoring, tests etc.)	None	N/A
Total cost per treatment/patient	£340,200 per first year, £1,024 for administration for the 20% who are not enrolled in the aHUS homecare initiative, £30 cost for a meningococcal vaccine	See above.

Table D9: Costs per treatment/patient associated with plasma therapy in adult patient in the cost-consequences model

Items	Value	Source
Cost of the comparator per treatment/patient	£31,148 (adult) and £45,240 (paediatric) per year	NHS reference cost of SA13A in 2011/2012 year for cost of session and weekly frequency based upon expert opinion; assumed to be more costly than average because whole plasma is used
Administration cost	Included in reference cost	See above
Training cost	0	N/A
Other costs (monitoring, tests etc.)	Included in reference cost	See above
Total cost per treatment/patient	£31,148 (adult) and £45,240 (paediatric) patient per year	See above

Health-state costs

12.3.7 If the cost-consequences model presents health states, the costs related to each health state should be presented in the table below. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-consequences model.

Table D10: List of health states and associated costs for adult patient (19 years old and over) in the cost-consequences model

Health states	Items	Value	Reference
Transplant	Cost of kidney transplant	£18,792	NHS reference costs of 2011/2012 year
	Annual transplant maintenance cost	£6,641	Economic models from NICE TA N85 (2006) inflated by PSSRU index
CKD stage 1-2	Estimated annual costs of consultations and medications under a formal referral strategy for the most severe patient	£960	Black et al. 2010, inflated by PSSRU index
CKD stage 3-4	Estimated annual costs of consultations and medications under a formal referral strategy for the most severe patient	£971	Black et al. 2010, inflated by PSSRU index
ESRF	Estimated annual costs of consultations and medications under a formal referral strategy for the most severe patient	£982	Black et al. 2010, inflated by PSSRU index
	Cost of dialysis	£23,300	NHS reference costs of 2011/2012 year

The model includes cost of managing CKD and costs associated with kidney transplant.

Costs of Managing CKD

For total health service costs by CKD stage, we used the results published by Black et al. (2010). Black estimated the costs of consultations and medications under a formal referral strategy for patients with markers of renal disease by CKD stage and level of comorbidity. Given the poor state of health of aHUS patients we used the highest estimates of annual cost (based on CKD with albumin–creatinine ratio > 300 mg/g and CVD) although costs are very similar for most CKD patients with any degree of significant co-morbidity. Black reports that the one-year cost for patients with CKD stages 1-2 were £840 and £854 for patients with CKD stages 3-4. These costs were inflated from 2006/7 prices to 2011/12 prices by applying PSSRU NHS cost inflator.

In the model alongside CKD costs plasma therapy cost is used for standard care. Estimates for plasma therapy costs are based on reference costs and were described in section 12.3.1. ESRF care costs also include the cost of dialysis that is based on reference costs and also described in section 12.3.1.

Transplantation costs

For transplanted patients, we used the annual average cost of maintenance treatment to be the £6,641 inflated by PSSRU index from NICE TA N85 "Immunosuppressive therapy for renal transplantation in adults" (2006). The cost per kidney transplant was assumed to a weighted average reference cost for 2011/2012, described above in section 12.3.1.

Adverse event costs

12.3.8 Complete table D9 to provide details of the costs associated with each adverse event included in the cost-consequences model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Eculizumab is generally very well tolerated. Adverse reactions were mostly mild to moderate in severity. The most commonly reported AEs from the two main eculizumab trials were headache, dizziness, nausea, and pyrexia, each occurring in 5% or more patients. Although almost all patients reported AEs in the aHUS studies, few were considered drug-related by the investigators.

In the two prospective aHUS studies, there was only one AE which led to treatment discontinuation, and this AE was deemed unrelated to study drug. The AE profile with eculizumab treatment of aHUS patients is therefore consistent with the safety profile with eculizumab previously reported in PNH patients.

Importantly, the AEs of SOC have never been evaluated in a similar manner. There has never been a clinical trial measuring the AE rate (or other outcomes) of plasma exchange, plasma infusion, dialysis or kidney transplant in patients with aHUS. The pre-treatment period of Legendre et al. was retrospectively analysed, so AEs were not recorded in the manner they would be in C08-002 or 003. Frequent and severe AEs have been documented for PE/PI in patients receiving this for all possible indications, as detailed elsewhere in the submission.

Since the AE profile is generally mild for eculizumab, and there is no specific trials source for SOC, the model does not include any health or cost implications for treatment-related AEs for either eculizumab or standard of care.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

All resource use costs included in the model are described in the preceding sections.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

All resource use costs included in the model are described in the preceding sections.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-consequences analysis.

The model structure was reviewed by clinical experts who found it to be valid. They also reviewed the use of the pre-treatment data from C08-002 and 003 to parameterise plasma exchange, plasma infusion, kidney transplant, and dialysis and found that approach to be valid.

Univariate sensitivity analyses of parameter inputs were conducted and are described later in this section.

Probabilistic sensitivity analysis was conducted and is described later in this section.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Probabilistic sensitivity analysis (PSA) was conducted. The PSA was run with 500 simulations based on varying all PSA parameters based on column four in Table D10: Summary of variables applied in the cost-consequences model. For eculizumab efficacy variation, a bootstrap with replacement method was used to non-parametrically vary efficacy and starting CKD stage. This process essentially redrew 37 patients iteratively from the trials data, allowing the same patient to be used multiple times, to assess stochastic variation. Given the small sample and unknown multinomial distribution of the underlying

states (a Dirichlet distribution could have been assumed, but the nonparametric bootstrap obviates making the underlying parametric assumption), the bootstrap was an efficient methodological option. SOC efficacy was varied based on the fixed effects specification regression model, specifically assuming a normal distribution around its mean (coefficient) and standard error to assess variation in the (sample mean) relationship between eGFR and days. Costs were varied based on a gamma distribution assuming standard deviations were equivalent to means (i.e., a coefficient of variation of unity). Parameters bounded [0,1] were assumed to have a beta distribution, using either sample size and a binomial assumption to calculate standard deviations or using standard deviations directly from the data source.

12.4.3 Complete the questions below as appropriate to summarise the variables used in the sensitivity analysis.

Table D11: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Age	23	12 - 45
Discount rate, costs and benefits	0.015/0.015	0.03/0.03
Discount rate, costs and benefits	0.015/0.015	0.03/0.015
Include C08-002 patients only	all	only 002
Include C08-003 patients only	all	only 003
Eculizumab reduces ESRF death transitional probability by 50%	0.051	0.025
SOC excess death, 6-month transitional probability (+/- 50%)	0.029	0.0145 - 0.0435
SOC likelihood of a 15 point EGFR drop, 6-month transitional probability (+/- 50%)	0.367	0.183 - 0.550
SOC transplant success transitional probability (+/- 50%)	0.25	0.125 – 0.375
SOC transplant excess mortality transitional probability (+/- 50%)	0.051	0.025 - 0.076
Health state costs (+/- 50%)	base	50%
Eculizumab price (+/- 10%)	£3,150	£2,835 - £3,465
Plasma exchange price (+/- 50%)	£15,574	£7,787 - £23,361
SOC health utility (varying Ecu health increment) (+/- 50%)	0.208	0.104 - 0.312
Eculizumab health utility (+/- 10%)	base	-10%
Alternative health utilities (EQ-5D scores at baseline)	base	Use EQ-5D distribution from trials (see section 12.5.3
ESRF excess mortality rate	base	0.026 - 0.079

Variables used in multi-way scenario-based sensitivity analysis

Multi-way sensitivity analysis was based on the following three high leverage, exogenous variables:

<u>Multi-way sensitivity analysis 1:</u>

- Age 45 at baseline;
- SOC health utility difference versus eculizumab (varying eculizumab health increment) (+50%); and

- SOC likelihood of a 15-point eGFR drop, 6-month transitional probability (-50%).

Multi-way sensitivity analysis 2:

- Eculizumab reduces ESRF death likelihood by 50%;
- 3% discount rate on costs; and
- SOC likelihood of a 15 point eGFR drop, 6-month transitional probability (+ 50%)

Variable values used in probabilistic sensitivity analysis

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Background mortality is not varied as these parameters are based on huge national samples. Patient weight intervals are not varied, given that the base case distribution reflects idiosyncratic expectations about use in England. The cycles of post-transplant care are not varied, given that there is uncertainty over the extent of the use of these products in an aHUS population.

12.5 Results of de novo cost-consequences analysis

Section 12.5 requires the sponsor to report the de novo cost-consequences analysis results. These should include the following:

- benefits
- costs
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean results (costs, QALYs)
- results of the sensitivity analysis.

Clinical outcomes from the model

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table D12: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Improvement in CKD of at least 1 stage	20/37 at week 64	16/37 at week 52**
QALYs (EQ-5D scores)	(0.30*17/37 + 0.13*20/37) = 0.208	0.215*

* See cell BR7 in the sheet entitled 'Ecu_Markov'. Model likely reflects a larger gain in utility because some SOC patients are expected to die within the first year.
** See cell A39 in the sheet entitled 'Ecu_trials_data'. Difference may be because of measurements at week 64 and week 52.

12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces for the two treatment groups are provided in Figure D6 and Figure D7 below.

Figure D6: Markov Trace for eculizumab-treated patients

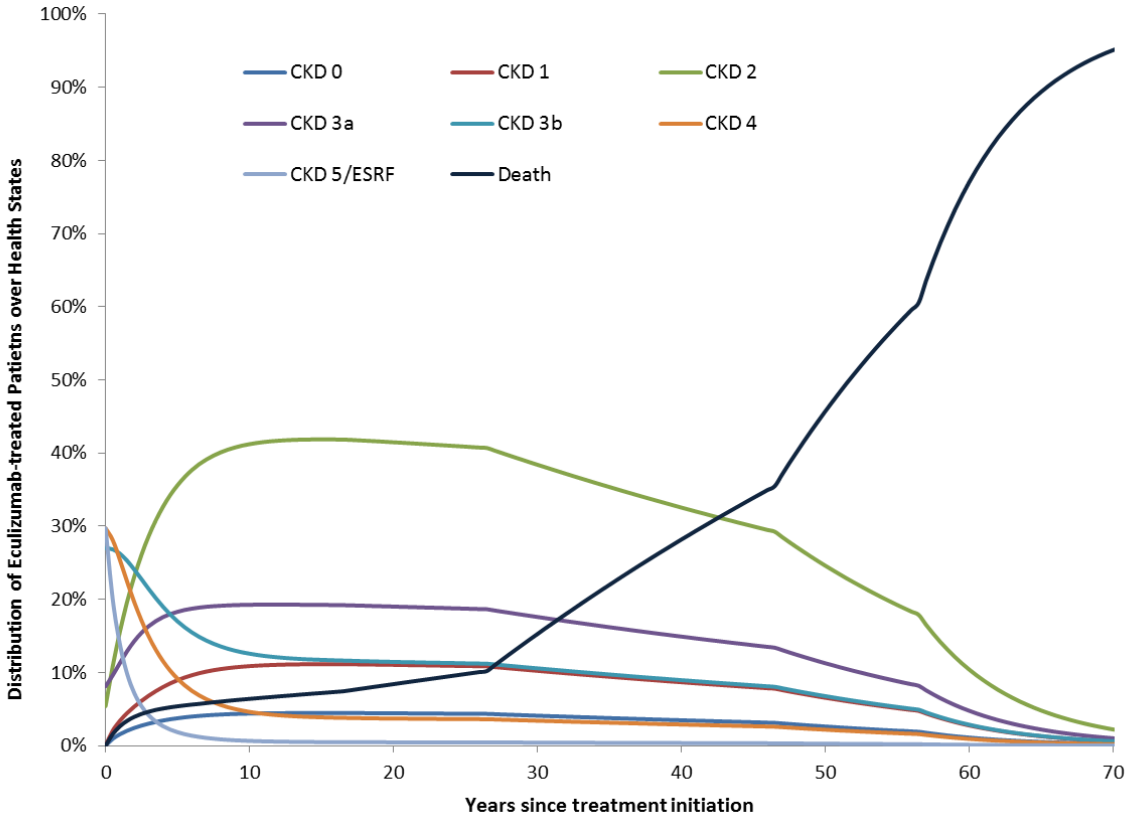
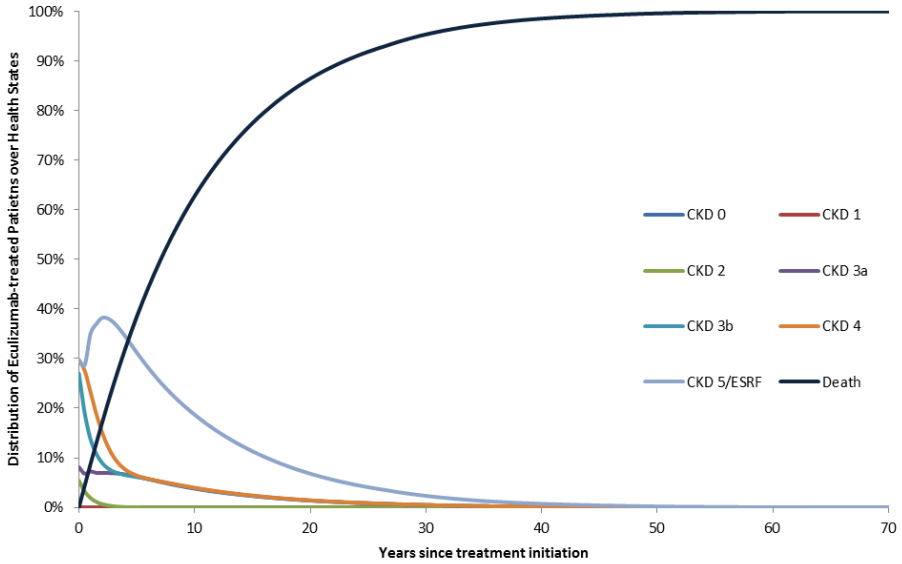


Figure D7: Markov Trace for SOC-treated patients



12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

CKD Stage Health Utility

Base Case

In Legendre et al. 2013, at the end of Table 2, the mean change in European Quality of Life Group 5 Dimensions Self-Report Questionnaire (EQ-5D) is presented for the two trials. In the base case analysis, we assume that every patient alive gets the increment evenly across the disease states.

The increment for all patients is 0.208 over the 64-week period, based on the weighted average calculation in Table D13. Note that though this is over a 64-week period, the results are similar by week 26 (0.201) in the Legendre publication, and in fact, the effect is evident before the end of month three in the C08-003 trial and before the end of month one in the 002 trial, and we assume that this effect occurs within six months on eculizumab and persists in the model. We use the increment in our 0.208 base case health utility analyses; we use the standard deviations from Table 2 in Legendre et al. 2013 and assume a normal distribution in the probabilistic sensitivity analysis for this variable.

Table D13: Measurement of eculizumab health utility increase over SOC

	Delta EQ-5D baseline to week 64 (a) [mean (SD)]	**Sample Size (b)**	**(a*b)**
Trial 1 (C08-002)	0.30 (0.05)	17	0.138
Trial 2 (C08-003)	0.13 (0.025)	20	0.070
		37	**Σ(a*b)**
	Increment for eculizumab in all states		**0.208**

Ideally, we would use baseline EQ-5D scores from Legendre et al., 2013 as the SOC scores, and add the 0.208 increment to them. However, those baseline scores are, by CKD stage (Table D14).

Table D14: Baseline (SOC-treated patients) Health Utility in C08-002 and CO8-003 Trials

Model State	**Health Utility** (annual increments)
CKD 0, 1, 2	0.845
CKD 3, 4	0.722
ESRF	0.558

Adding the 0.208 increment for eculizumab to the baseline CKD 0-2 state would produce a health utility above 1. Accordingly, we took the year one eculizumab scores and deducted the 0.208 increment to estimate SOC scores. As such, we use the week 52 health utility scores for eculizumab, per Table D15 below, in the base case.

Table D15: Week 52 (eculizumab-treated patients) Health Utility in 002 and 003 Trials

Model State	**Health Utility** (annual increments)
CKD 0, 1, 2	1.000

Model State	Health Utility (annual increments)
CKD 3, 4	0.870
ESRF	0.867

We use the same week 52 health utility scores for eculizumab less the 0.208 decrement for SOC health utilities, per Table D16 below, in the base case.

Table D16: Health Utility for SOC treated patients (Week 52 in C08-002 and C08-003 Trials minus the 0.208 decrement)

Model State	Health Utility (annual increments)
CKD 0, 1, 2	0.792
CKD 3, 4	0.662
ESRF	0.659

The SOC and eculizumab patients have different health utilities for the same CKD state. However, it should be remembered that the SOC patients do not have their underlying complement disease treated, and are expected to continue to have a high rate of non-renal TMAs which would cause substantial disability.

Health Utility Sensitivity Analysis: Alternative Health Utilities

The base case may understate the gain in health utility from treating with eculizumab. Recall that the base case is based on health utility measured at baseline versus health utility measured at 64 weeks after eculizumab therapy initiation from Legendre et al. 2013. The change in EQ-5D scores is based on the migration to better CKD stages and from a reduction in other disease burden (for example, on clinical expert believed that it was likely that there are subclinical micro-TMAs which make a patient feel poorly when their underlying complement disorder is left untreated, but which would disappear with use of eculizumab). It is clear from the trials data that eGFR (and thence CKD stage distribution) improves for patients on eculizumab therapy relative to baseline. But, left untreated, our pre-treatment data analysis of the relationship between eGFR and time indicates that CKD stages are worsening for patients on SOC. In other words, the baseline distribution would be worse by week 64, and would continue to worsen for surviving patients. The base case assumes the baseline to week 64 gain in health utility is a static increment, when in fact the SOC-treated patients would likely continue to decline, and the increment would increase for patients who were alive.

Accordingly, we conduct a sensitivity analysis. In the two prospective aHUS eculizumab clinical trials, quality of life changes were measured by EQ-5D scores at baseline and at the end of the first year on therapy. We used the baseline EQ-5D scores by CKD stages (0-2, 3a-4 and 5 [ESRF]) as a measure of the health state by stage of non-eculizumab-treated patients throughout the model. Baseline figures are provided below:

Baseline EQ-5D scores by CKD stages (1-2, 3-4 and 5 [ESRF]) used as a measure of the health state by stage of non-eculizumab-treated patients.

- CKD Stage 1-2: 2 patients (2 with data); mean = 0.845, standard deviation (sd) = 0.22.
- CKD Stage 3-4: 24 patients (24 with data); mean = 0.722, sd = 0.345.
- CKD Stage 5 (ESRF): 11 patients (10 with data); mean = 0.558, sd = 0.343.

Day 364 EQ-5D scores by CKD stage as the measure of health status for eculizumab-treated patients where the CKD stage was recorded for Day 364.

- CKD Stage 1-2: 5 patients (3 with data); mean = 1.0, sd = 0. Please note: no Day 182 scores for the 2 patients without Day 364 scores.
- CKD Stage 3-4: 16 patients (15 with data); mean = 0.87, sd = 0.189. Please note: last observation carried forward (LOCF) for 1 patient from Day 182 with a score of 0.796 of CKD 3-4 at Day 182.
- CKD Stage 5 (ESRF): 4 patients (4 with data); mean = 0.867, sd = 0.18.

Transplant Health Utility

After one cycle in transplant, successfully transplanted patients are assumed to move to CKD stage 3a (see the section entitled "SOC: Kidney transplant outcomes—the transitions from kidney transplant to CKD5 (failure), death, or success (CKD 3a)"). We assume that they take on the health utility for the CKD 3a state. In one large study evaluating 4,488 graft recipients with no aHUS, the mean eGFR was 51.2 ml/min/1.73m^2 at 3 months following transplantation and 60% of patients had CKD stage 3 at 12 months following transplantation.(Marcen et al 2010)

12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The outcomes-based analysis does not apply for our model.

12.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table D17: Summary of quality-adjusted life year (QALY) gain by health state

Health state	QALY Eculizumab	QALY SOC	Increment	Absolute increment	% absolute increment
CKD 0-1-2	18.82	0.04	18.78	18.78	74.5%
CKD 3-4	11.67	2.04	9.62	9.62	38.2%
ESRF	0.51	2.72	-2.22	-2.22	-8.8%
Transplant	0.00	0.96	-0.96	-0.96	-3.8%
Dead	0.00	0.00	0.00	0.00	0.0%
Total	30.99	5.77	25.22	25.22	

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Base-case analysis

12.5.6 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis.

Table D18: Base-case results

	Total per patient cost (£)
Eculizumab	[redacted]

	SOC	**£322,313**

12.5.7 Report the total difference in costs between the technology and comparator(s).

[redacted]

In Table D19, we provide details of the costs for the technology and its comparator by category of cost in a six-month interval. We include the price of eculizumab, and vials consumed in the induction and maintenance periods. There is no specific testing or monitoring requirements for eculizumab patients. About 80% of patients are expected to be enrolled in a homecare program which will cover the costs of their infusion administrations. Patients enrolled in the homecare programme will incur no administration costs to the NHS as Alexion funds aHUS homecare programme in England. Patients not enrolled would be expected to incur such costs. Chair time for an eculizumab infusion is 30 minutes. For those being infused using NHS resources, we assume that the infusion costs are £197 per session, per "Deliver simple parenteral chemotherapy first attendance (Currency Code SB12Z)." We assume 13 administrations per 6 months.

Meningococcal vaccine is routine at induction. We assume the cost of Menveo (meningococcal A, C, W135 and Y conjugate vaccine) at £30.00 per the British National Formulary, August 2013, for each eculizumab patient.

Plasma exchange technology costs already include administration and other costs; see Section 12.3.1 describing their derivation.

Table D19: Summary of costs by category of cost per patient

Item	Cost eculizumab	Cost SOC	Increment
Technology cost			
Price of biologic eculizumab per vial	£3,150		
Induction doses (1/2 year)	42.9		
Maintenance doses (1/2 year)	39.8		
SOC therapy cost (PLEX), adult (1/2 year)		£15,574	
SOC therapy cost (PLEX), child (1/2 year)		£22,620	
Mean total treatment cost, induction, per six months, adult	£135,135	£31,148	£103,987
Mean total treatment cost, maintenance per six months, adult	£125,370	£31,148	£94,222
Administration cost, per six months	£512	*	*
Monitoring cost	**	*	*
Tests	**	*	*
Meningococcal vaccine	£30	0	£30
Total, adults (induction) (1/2 year)	£135,677	£31,148	£104,529
Total, adults (maintenance) (1/2 year)	£125,882	£31,148	£94,734

* Plasma exchange technology costs include administration and other costs; see section describing their derivation.
** There is no specific testing or monitoring requirements for eculizumab patients.
Note: About 80% of patients will be enrolled in a homecare program which will cover the costs of their infusion administrations. These patients will have no administration cost since Alexion pays for the homecare program.

Chair time for an eculizumab infusion is 30 minutes. For those being infused in a facility, we assume that the infusion costs are £197 per session, per "Deliver simple parenteral chemotherapy first attendance (Currency Code SB12Z)." We assume 13 administrations per six months. Costs of SOC are for adults only.
Note: Meningococcal vaccine is routine at induction. We assume the cost of Menveo (meningococcal A, C, W135 and Y conjugate vaccine) at £30.00 per the British National Formulary, August 2013."
Note: The SOC plasma price for children is £22,608 per six months.

12.5.8 If appropriate, provide details of the costs for the technology and its comparator by health state.

Table D20: Summary of costs by health state per patient

Health state	Cost SOC	Cost ECU	Incremental (ECU - SOC)	Percentage of total
CKD 0-1-2	£2,435	[redacted]	[redacted]	0.2%
CKD 3-4	£113,701	[redacted]	[redacted]	-1.0%
ESRF	£100,372	[redacted]	[redacted]	-0.8%
Transplant	£103,437	[redacted]	[redacted]	-1.0%
Transplant success, ongoing costs	£2,367	[redacted]	[redacted]	0.0%
Biologic (Ecu) Cost	£0	[redacted]	[redacted]	102.7%
Total:	£322,313	[redacted]	[redacted]	

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state.

N/A as eculizumab costs do not vary by health state.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event

Adverse events are not included in the model, per prior discussion points, namely that eculizumab in aHUS is associated with mild AEs and SOC and its various components have never had their adverse event rates measured in a clinical trial setting.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table below.

Table D21: Results of One-Way Sensitivity Analysis

Parameter	Base case	Sensitivity	SOC Costs	Ecu Costs	Incremental Costs	SOC Benefits	Eculizumab Benefits	Incremental Benefits
Base case	All	None	£322,313	[redacted]	[redacted]	5.773	30.995	25.221
Age	28	45	£307,146	[redacted]	[redacted]	5.490	23.272	17.782
	28	12	£325,495	[redacted]	[redacted]	5.833	36.825	30.992
Discount rate, health utility	0.015	0.03/0.03	£287,867	[redacted]	[redacted]	5.137	22.701	17.564
Discount rate, costs and benefits	0.015	0.03/0.015	£287,867	[redacted]	[redacted]	5.773	30.995	25.221
Include C08-002 patients only	all	only 002	£319,595	[redacted]	[redacted]	5.726	31.868	26.142
Include C08-003 patients only	all	only 003	£324,623	[redacted]	[redacted]	5.814	30.851	25.037
Eculizumab reduces ESRF death likelihood by 50%	0.052	0.026	£322,313	[redacted]	[redacted]	5.773	31.927	26.153
SOC excess death, 6-month tp (+/- 50%)	0.04	0.06	£286,328	[redacted]	[redacted]	5.098	30.995	25.896
	0.04	0.02	£370,431	[redacted]	[redacted]	6.679	30.995	24.316
SOC likelihood of a 15 point EGFR drop, 6-month tp (+/- 50%)	0.367	0.550	£318,267	[redacted]	[redacted]	5.664	30.995	25.330
	0.367	0.183	£329,588	[redacted]	[redacted]	5.982	30.995	25.012
SOC tranplant success rate (+/- 50%)	0.25	0.375	£325,582	[redacted]	[redacted]	5.838	30.995	25.157
	0.25	0.125	£317,881	[redacted]	[redacted]	5.679	30.995	25.316
SOC transplant excess mortality rate (+/- 50%)	0.051	0.076	£303,079	[redacted]	[redacted]	5.415	30.268	24.853
	0.051	0.025	£348,416	[redacted]	[redacted]	6.260	31.972	25.712

Parameter	Base case	Sensitivity	SOC Costs	Ecu Costs	Incremental Costs	SOC Benefits	Eculizumab Benefits	Incremental Benefits
Health state costs (+/- 50%)	base	50%	£402,602	[redacted]	[redacted]	5.773	30.995	25.221
	base	-50%	£242,024	[redacted]	[redacted]	5.773	30.995	25.221
Eculizumab price (+/- 10%)	£3,150	£3,465	£322,313	[redacted]	[redacted]	5.773	30.995	25.221
	£3,150	£2,835	£322,313	[redacted]	[redacted]	5.773	30.995	25.221
Plasma exchange price (+/- 50%)	£15,574	£23,361	£471,827	[redacted]	[redacted]	5.773	30.995	25.221
	£15,574	£7,787	£241,446	[redacted]	[redacted]	5.773	30.995	25.221
SOC health utility (Ecu health increment)	0.208	0.312	£322,313	[redacted]	[redacted]	4.865	30.995	26.130
	0.208	0.104	£322,313	[redacted]	[redacted]	6.682	30.995	24.313
Eculizumab health utility (+/- 10%)	base	10%	£322,313	[redacted]	[redacted]	6.532	30.995	24.462
	base	-10%	£322,313	[redacted]	[redacted]	5.014	30.995	25.980
Alternative health utilities (EQ-5D scores at baseline for SOC)	base	Alt	£322,313	[redacted]	[redacted]	5.632	30.995	25.362
ESRF mortality rate	0.052	0.079	£269,019	[redacted]	[redacted]	4.783	30.995	26.212
	0.052	0.026	£408,721	[redacted]	[redacted]	7.384	30.995	23.611

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in Section 12.4.3.

Two multi-way sensitivity analyses were conducted based on the following scenarios:

Multi-way sensitivity analysis 1:

- Age 45 at baseline
- SOC health utility difference versus eculizumab (varying eculizumab health increment) (+50%)
- SOC likelihood of a 15-point eGFR drop, 6-month transitional probability (-50%)
- Results:
  - [redacted]
  - Incremental QALYs: 16.71

Multi-way sensitivity analysis 2:

- Eculizumab reduces ESRF death likelihood by 50%
- 3% discount rate on costs
- SOC likelihood of a 15 point eGFR drop, 6-month transitional probability (+50%)
- Results:
  - [redacted]
  - Incremental QALYs: 23.47

12.5.13 Present results of the probabilistic sensitivity analysis described in table below.

Table D22: Results of the Probabilistic Sensitivity Analysis

Analysis of Simulation Results	Mean (95% CI: Lower Bound, Upper Bound)
SOC Costs	£328,986 (£170,557 - £650,831)
[redacted]	[redacted]
SOC Benefits	5.9 (2.6 - 8.7)
Eculizumab Benefits	31 (28.4 - 32.7)
[redacted]	[redacted]
Incremental (Eculizumab - SOC) QALYs	25.1 (21.2 - 28.8)
SOC Life years	10.6 (7.4 - 14.2)
Eculizumab Life Years	47.9 (44.1 - 50.3)
SOC QALYs in ESRF	2.8 (0.6 - 4.3)
Eculizumab QALYs in ESRF	0.5 (0.1 - 1.2)
Incremental (Eculizumab - SOC) Life Years	37.3 (32.1 - 41.6)
Incremental (Eculizumab - SOC) QALYs in ESRF	-2.3 (-3.9 - -0.1)

Histograms reporting the distribution of the 500 simulations for the following appear in the figures below.

- Figure D8: Incremental (Eculizumab - SOC) Costs
- Figure D9: Incremental (Eculizumab - SOC) QALYs
- Figure D10: Incremental (Eculizumab - SOC) Life Years
- Figure D11: Incremental (Eculizumab - SOC) QALYs in ESRF

[redacted]

Figure D9: Incremental (Eculizumab - SOC) QALYs

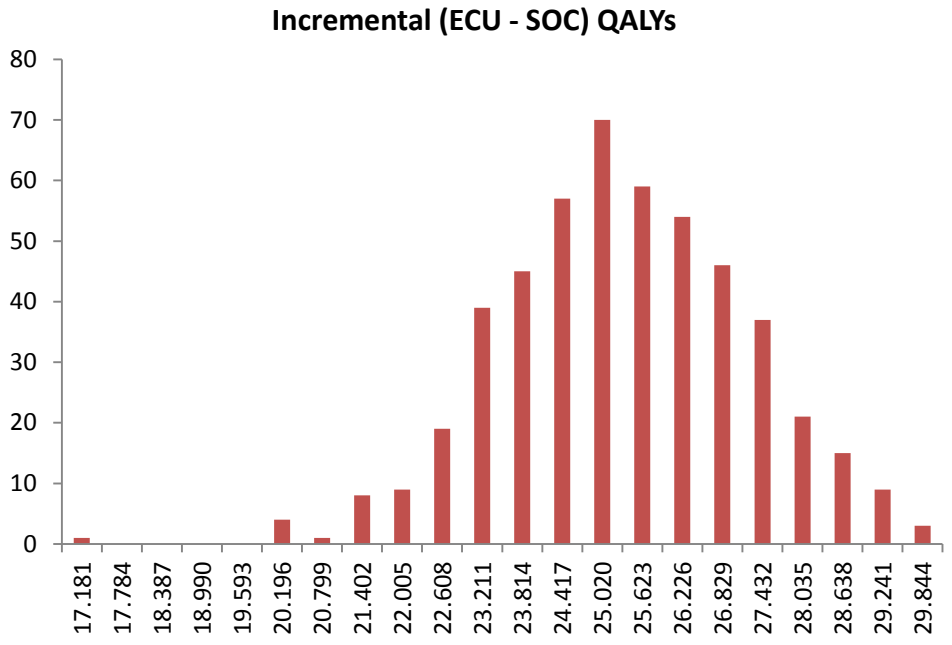


Figure D10: Incremental (Eculizumab - SOC) Life Years

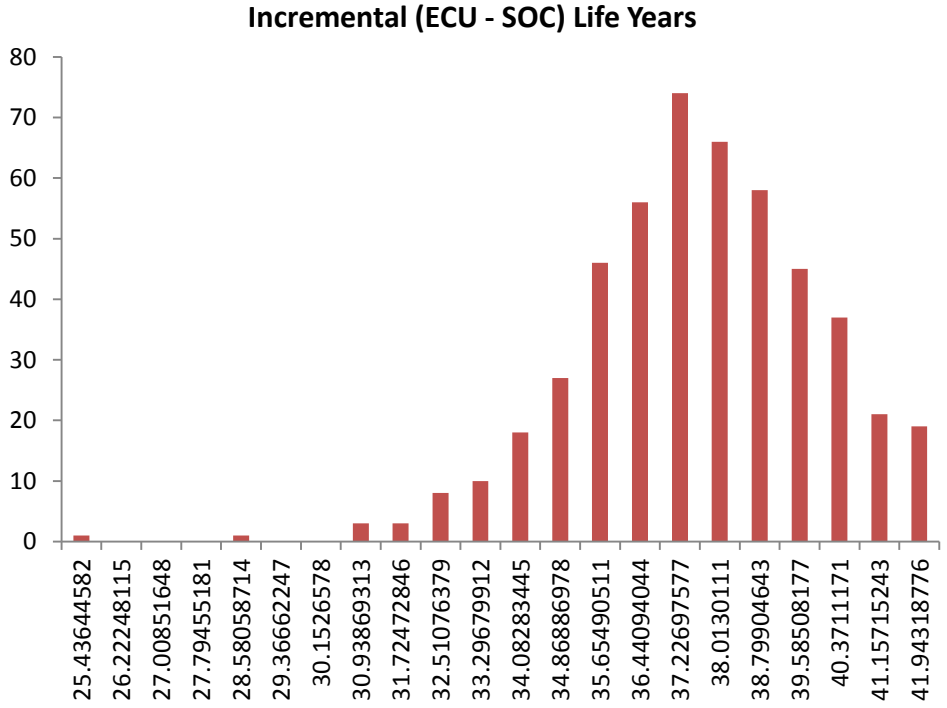
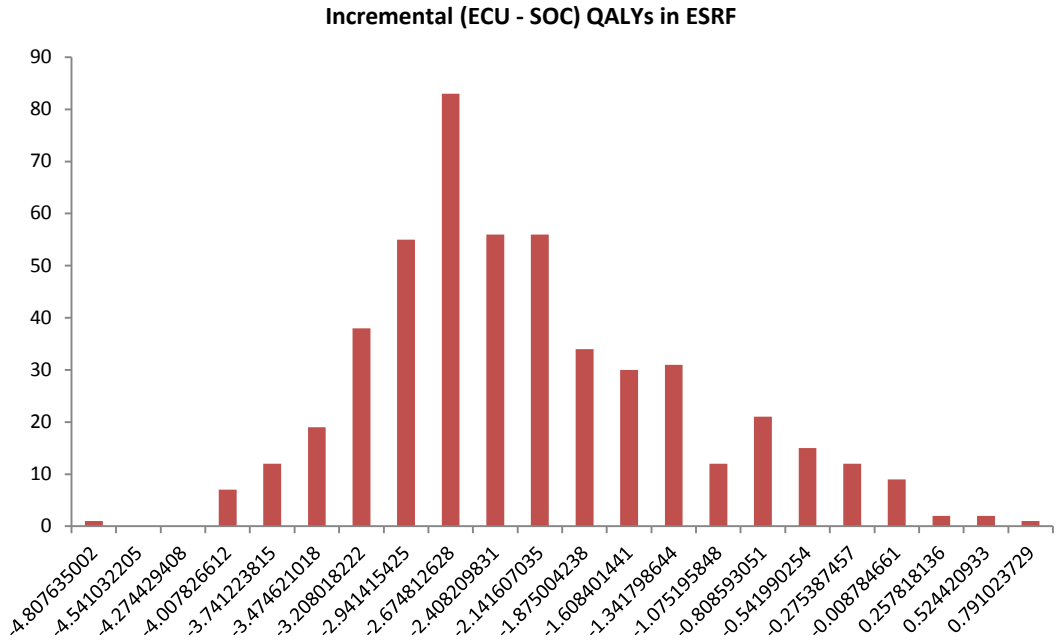


Figure D11: Incremental (Eculizumab - SOC) QALYs in ESRF



12.5.14 What were the main findings of each of the sensitivity analyses?

Overall, in each of the sensitivity analyses, the distributions are symmetrical. In the vast majority of simulation results, eculizumab confers large gains in QALYs and life expectancy, as well as much less time in ESRF.

12.5.15 What are the key drivers of the cost results?

The three factors most associated with incremental cost increases are:

1. Initiating patients at age 12 on average
2. Increasing the eculizumab price by 10%
3. Eculizumab reducing the ESRF death likelihood by 50%

The three factors most associated with incremental cost decreases are:

1. Discounting costs at 3%
2. Initiating patients at age 45 on average
3. Decreasing the eculizumab price by 10%

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

There are no additional results that should be reported.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified.

No subgroup analysis was performed.

12.6.2 Define the characteristics of patients in the subgroup(s).

No subgroup analysis was performed.

12.6.3 Describe how the subgroups were included in the cost-consequences analysis.

No subgroup analysis was performed.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis).

No subgroup analysis was performed.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

The data are limited for modelling outcomes for the full sample in aHUS, an ultra-rare disease, arguably to the point that one could argue that valid inferences from the model are not possible. Subgroup analysis would parse an already ultra-thin data source, and so were not performed

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

We used the TMA registry data from Coppo et al and Hovinga et al to validate both the CKD based model and non-renal mortality. While use of registries have inherent limitations to estimate incidence and prevalence of clinical complications, we believe both of these TMA databases most closely match the eculizumab aHUS patient by consecutively and non-selectively recruiting patients who reflect the current diagnosis pathway for aHUS into the registry from validated sources, evidence of TMA at presentation, any TMA-related organ damage and measured ADAMTS13 activity to define aHUS vs. TTP patients.

There are also published event-time data from aHUS registries reporting the progression to ESRF and mortality which show declining renal function in the first one to three years comparable with predictions in this submission model. Specifically, Legendre et al. state: "ESRD or death occurs in approximately 33% to 40% of patients during the first clinical manifestation." Indeed, data from Caprioli et al (Blood 2006) reported approximately 33% of patients reach ESRD or die following the first clinical presentation of TMA (assumed to be within 1 year) and Noris et al (CJASN 2010) reported approximately 56% at 3 years. Both publications report 8-11% mortality in approximately 1-3 years. We note that both these publications report on data from the HUS/TTP international registry and isolate TMA patients with acute renal failure for their estimations. Fremeaux-Bacchi et al. (CJSAN 2013) reported from a French population and report 56% of adults and 29% of children require renal replacement or died within 1 year of follow up. They reported 5-year survival without ESRF was 64% in children and 36% in adults. On the joint end-point of ESRD or death, our model predicts 54.6% at year 1 and 72.9% at year 2; note that at baseline in our model, 29.7% are already in ESRD per the trials C08-002 and 003. Interestingly Fremeaux-Bacchi et al reported a mortality of 7.8% and 1.6% at the end of follow up.

These three aHUS registries reported lower rates of ESRF and mortality > 5 years follow up compared to our model and what is reported in both the Coppo and Hovinga TMA registries. However we note some of the limitations and assumptions between our model and the aHUS renal-focused registries that may account for some differences in survival analysis outcomes.

- First, the three renal-focused aHUS registries did not enrol consecutive patients as they presented with aHUS. These registries relied on physicians to enrol patients. Considering the high rate of early mortality, our assumption

is that physicians did not enrol patients who died early in their care, leading to a survival bias at study entry.

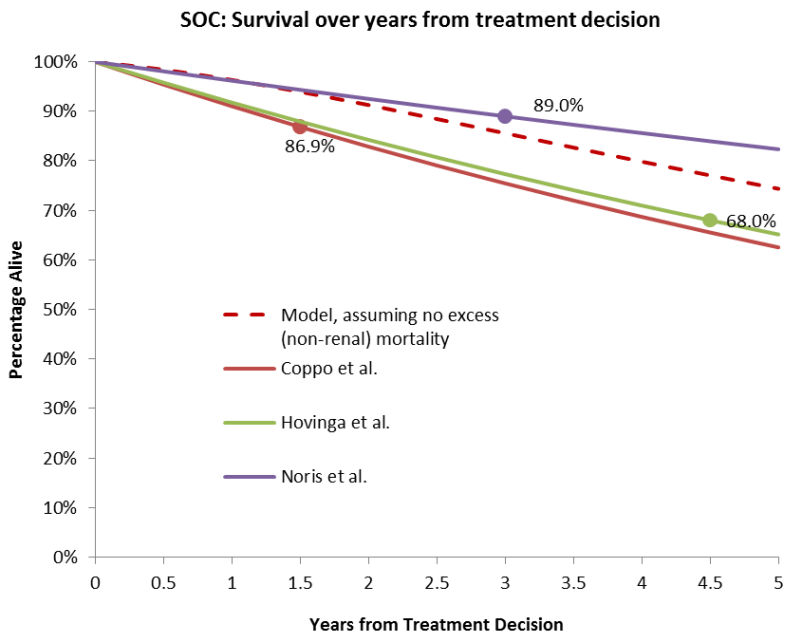
- Second, the physicians in the aHUS registries also may not have followed up on patients with other organ impairment or damage, given that the study involved a patient population with ultra-rare disease who were dispersed across multiple countries. By design, Kaplan Meier analysis censors those lost to follow-up, and does not assume that these patients are alive or did not progress to ESRF. Reported results could underestimate the number of deaths.

- Third, the renal focused aHUS registries may not have followed up on patients on dialysis and therefore may not have captured the high rate of mortality on dialysis over time. For example, Fremeaux-Bacchi et al reported a lower mortality than our model predicts and other aHUS registries report. However the investigators lost patients to follow-up once on dialysis. Accordingly, these studies often presented ESRF and death as a joint endpoint. Their death outcomes would be underestimated by censoring these patients.

In contrast, both the Coppo et al and Hovinga et al registries present a “real world” expectation of aHUS presentation and outcomes. Both registries present a large “all comers” sample who are defined by the differential diagnostic criteria used to identify patients who would be eligible for eculizumab and currently receive standard of care including PE/PI. The registries include patients from disease onset. They do not limit patients to voluntary patient enrolment by the treating physician. Based on these points, the use of the Coppo and Hovinga dataset is a more reliable dataset.

Below we highlight the mortality due to renal death in our model (dashed red line) compared to Noris et al (Figure D12). As described above the aHUS registries such as Noris model predict a lower mortality, possibly due to selection bias and lack of follow-up time. Coppo and Hovinga, registries that follow consecutive TMA patients with any organ damage, both reported a similar mortality curve over time. We used these curves to support our model of non-renal TMA mortality and over mortality. Therefore the patients in the eculizumab clinical trial demonstrate an estimated mortality aligned with reported mortality in two large TMA registries.

Figure D12: Comparison of Modelled and Reported Mortality



With regards to validating our eculizumab CKD stage outcomes, these are derived directly from the patient level clinical trial data. With regards to mortality, the eculizumab model predicts 1.7 deaths at three years, assuming a starting cohort of 37 patients. One patient death was observed in C08-002 and 003, deemed not related to the study drug. There could be a beneficial effect of eculizumab in CKD 5, which we test in a sensitivity analysis. Certainly, there would be expected benefits to treating a patient's underlying complement disorder when that patient would be on dialysis, considering the effect of TMA events for those in dialysis.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-consequences analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published literature assessing the costs of eculizumab vs. SOC.

To compare the size of the QALY gain predicted by our model, we compare versus results reported in Tufts University's Cost-effectiveness Registry, which offers systematic review of cost-effectiveness results. Table D23 reflects QALY gains for select interventions which were presented in a league table format. (https://research.tufts-nemc.org/cear4/Resources/LeagueTable.aspx, last accessed 9/10/2013). Selection criteria include studies published since 2003 in a journal whose impact factor is greater than or equal to 10. Changes in QALYs ranged from -0.05 (Heparin sodium and alteplase for haemodynamically stable patients with a sub-massive pulmonary embolism and right ventricular dysfunction) to 3.0 (implantable cardioverter defibrillator to prevent sudden cardiac death for patient who are at risk for sudden death due to left ventricular systolic dysfunction). The gains of eculizumab for aHUS should be considered in comparison to results such as these.

Table D23: Comparative QALY gains from select cost-effectiveness analyses publications

Intervention	Change in QALY	Source
Disease-modifying anti-rheumatic drugs compared to the traditional pyramid strategy for newly diagnosed rheumatoid arthritis patients	0.30	Finckh. Annals of Internal Medicine 2009
Daily enteric-coated aspirin compared to no aspirin for men age 55 or older with Barrett's esophagus to prevent esophageal cancer	0.19	Hur. Journal of the National Cancer Institute 2004
Early surgery compared to prolonged conservative care to treat patients with sciatica from lumbar disc herniation	0.02 to 0.04	van den Hout. BMJ 2008
Training for the caregivers of stroke patients compared to no training	0.00	Patel. BMJ 2004
Coumadin (Warfarin) compared to aspirin for 70 year-olds with atrial fibrillation	0.81	O'Brien. JAMA 2005
Diabetes education and self management compared to standard care for patients newly diagnosed with type 2 diabetes	0.04	Gillett. BMJ 2010
Daily dialysis compared to dialysis every other day for 60 year-old critically ill men with kidney injury	2.14	Desai. Archives of Internal Medicine 2008
ICD (implantable cardioverter defibrillator) compared to current standard of care to prevent sudden cardiac death for patient who are at risk for sudden death due to left ventricular systolic dysfunction	3.00	Sanders. New England Journal of Medicine 2005
HIV counselling, testing, and referral compared to current standard of care in high risk populations (HIV annual incidence 1.2% and prevalence of undiagnosed HIV 0.3%)	0.03	Paltiel. New England Journal of Medicine 2005
Spine surgery compared to non-operative treatment for adult patients with confirmed spinal stenosis and spinal nerve-based (radicular) leg pain	0.17	Tosteson. Annals of Internal Medicine 2008
Annual CT screening compare to no screening for 60 year-old heavy smokers who are eligible for lung reduction surgery	0.04	Mahadevia. JAMA 2003
Screening for osteoporosis with a bone densitometry and osteoporosis treatment compared to no densitometry or treatment for men age 65 and older with no prior fracture	0.03	Schousboe. JAMA 2007
Heparin sodium and alteplase compared to heparin sodium for haemodynamically stable patients with a sub-massive pulmonary embolism and right ventricular dysfunction	-0.05	Perlroth. Archives of Internal Medicine 2007
Annual compared to tri-annual rapid HIV screening in moderate to low risk populations	-0.003	Paltiel. Annals of Internal Medicine 2006

12.8.2 Is the cost-consequences analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The model's strengths include that fact that eculizumab and SOC efficacy were parameterized with patient-level clinical trials data. For eculizumab, more than three years of data are available for some patients. Published literature, though sparse, has been systematically used to populate the model. Incremental benefits are large in favour of eculizumab in all scenarios.

The model, and the data that support, the model have a number of limitations:

- Extreme difficulty exists with using a standard health technology assessment approach in modelling an ultra-orphan condition due to sparse data on current practices, lack of aHUS-specific or appropriately severity-adjusted NHS costing categories, and the limited number of patients in clinical trials. For example, the relatively small number of patients in the clinical trials makes any movement of one or two patients between CKD states have a relatively large effect on incremental effects.

  The EQ-5D scores recorded in the trials do not match well with values reported in the literature (e.g. relatively high EQ-5D scores were seen for patients with ESRF who were treated with eculizumab [observations of 1.0, 1.0 and 0.844 and 0.706). One expert speculated that eculizumab could improve quality of life in patients be obviating subclinical micro-TMAs, which could explain the large increase in health utility. Also, the psychological burden of plasma exchange is great, and removing that likelihood could greatly improve patients' HRQL.

- Non-fatal TMAs that affect non-renal function are an important part of the disease, but insufficient data were available to include them as distinct health states.

- The design and selection criteria for the aHUS and TMA registries are not aligned. The latter are a better approximation of the patients who would receive eculizumab.

- The economic model does not include productivity benefits or other indirect costs, though these are expected to be large and in favour of eculizumab.

- The model utilises eculizumab treatment data from both clinical studies C08-002 and C08-003. The investigators of the trials reported "Earlier intervention with eculizumab (i.e., a shorter interval between the current clinical manifestation of atypical haemolytic–uremic syndrome and initiation of treatment) was associated with significantly greater improvement in the estimated GFR in both trials."(Legendre et al, 2013) With increased disease awareness, earlier diagnosis and intervention and the establishment of specialist treatment services it is anticipated that patients will receive

eculizumab treatment much earlier than occurred in some of the patients enrolled in the trial and greater eGFR gains are likely to occur in clinical practice. For this reason, the renal benefits in the model for eculizumab are considered to be underestimated.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A registry could be set up in the UK measuring effects in patients initiating eculizumab.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

An epidemiological approach, based on the overall population of England, was used to determine the expected financial implications, commonly known as a budget impact model (BIM), associated with public funding for eculizumab for the treatment of aHUS over a five-year time period, from the beginning of 2013 to the end of 2017. Specific parameters and calculations used in the BIM are described in detail in the sections below.

Note about Rounding: Please note that throughout this section, and in the corresponding budget impact model (BIM) Excel spreadsheet that contains the BIM itself (Appendix 17.9), exact calculations were computed in the assessment of budget impact so no rounding is performed on the numbers included in the equations with two exceptions: 1) the "Total Country Population" values and 2) the final "Cost of Treatment" calculations. For both of these values, decimal points are displayed. Output for all others numbers in the model are displayed as integers and presented with zero decimal places showing. As a result, some computations may appear incorrect in the spreadsheet and seem to be off by a factor of "1"; however, this is due to rounding only as the numbers themselves are correct.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

Total English Population

The 2010 estimate of the English population, from the Office for National Statistics[4], was 52.6 million. The annual growth rate of the population was estimated to be 1.008, which was calculated as average of annual growth rates from 2005 to 2010 for the English population, also from the Office for National Statistics.[5] Using this growth

[4] From "Mid-2002 to Mid-2010 Subnational Population Estimates revised in light of the 2011 Census", specifically Table 4. Mid-2010 Population Estimates: England; estimated resident population by single year of age and sex; revised in light of the 2011 Census, available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population#tab-data-tables, last accessed 6/17/2013.

[5] From "Mid-2002 to Mid-2010 Subnational Population Estimates revised in light of the 2011 Census", specifically Table 4. Mid-2010 Population Estimates: England; estimated resident

rate, the English population for 2013 (Year 1 in the BIM) is estimated to be 53.9 million persons, increasing to 55.6 million in 2017 (Year 5 in the BIM).

Prevalence and Incidence of aHUS in England

As expected with an ultra-rare disease, data on the prevalence of aHUS are extremely limited. Our base case prevalence estimate is 5.5 persons per million, which is based on the prevalence of aHUS reported in NHS North East, specifically in the Newcastle area as reported by Professor Tim Goodship in a previous submission to the Advisory Group for National Specialised Services (AGNSS) in 2012. Our base case incidence estimate is 0.6 persons per million. This assumption is based on data originally received from the paediatric and adult renal units in the UK for prevalent and incident patients in 2009 to 2010 (data provided by Professor Tim Goodship, 2012) and projected to reflect recent data from English aHUS cases newly diagnosed in 2013. The data presented within the BIM represent the most recent understanding of the prevalence and incidence of aHUS within England. There is still some uncertainty that all cases have been identified and diagnosed within England, hence the model predicts that some existing "undiagnosed" cases will be diagnosed during the five-year period of the BIM. In the baseline year (Year 1) of the BIM, prevalent patients are calculated. Incident patients are modelled as entering the patient pool at the beginning of the next year (Year 2).

Due to lack of published data on adult incidence and prevalence of aHUS, for purposes of this model, we assume that the probability of an aHUS clinical manifestation is equally likely to occur in children and adults. Therefore, the estimated prevalence is assumed to be 5.5 aHUS patients per million for both children and adults. This approach is supported by the wide age spread of patients with aHUS observed in the eculizumab clinical trials: the age range of patients enrolled in prospective study C08-002 was 17 to 68 years of age; in the prospective C08-003 study, the age range was 13 to 63 years.

The total number of treatable aHUS patients is tracked in the BIM in terms of prevalence, plus incidence, minus mortality. Use of mortality estimates for purposes of the BIM is explained further below. [redacted], per row 9 on the sheet entitled "Ecu Scenario" in the electronic version of the model.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Diagnosed and Treated Patients

The percentage of aHUS patients diagnosed and treated each year is expected to increase gradually over time as diagnostic methods evolve, and physician and patient awareness about the disease increases. Based on Alexion's recent experience in another ultra-rare disease, Paroxysmal Nocturnal Haemoglobinuria (PNH), and our experience to date with aHUS, we assume the schedule of market uptake (treatment rate amongst diagnosed patients) for eculizumab depicted in Table D24 below, rows 1 and 2. For purposes of the BIM, patients who are not expected to

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population by single year of age and sex; revised in light of the 2011 Census, available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population#tab-data-tables, last accessed 6/17/2013.

be treated with eculizumab are assumed to receive standard of care (SOC) prior to the availability of eculizumab.

Specifically, two scenarios are included in the BIM: one where eculizumab is recommended for use, called the "Eculizumab Available Scenario", and another where it is not recommended, called the "Eculizumab Not Available Scenario". The difference in the calculated budget in these two scenarios is the net budget impact.

The description of the BIM structure in this section will focus on the "Eculizumab Available Scenario", as the "Eculizumab Not Available Scenario" is identical in all aspects except for the differences in the distribution of initiated treatments outlined below. Note that patients in both scenarios receive either eculizumab or SOC prior to the availability of eculizumab.

Table D24: Estimated Market Uptake of Eculizumab in aHUS

	Year 1 (2013)	**Year 2 (2014)**	**Year 3 (2015)**	**Year 4 (2016)**	**Year 5 (2017)**
Eculizumab Available Scenario					
1) eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2) SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Year 1 (2013)	**Year 2 (2014)**	**Year 3 (2015)**	**Year 4 (2016)**	**Year 5 (2017)**
Eculizumab Not Available Scenario					
3) eculizumab	0.0%	0.0%	0.0%	0.0%	0.0%
4) SOC	100.0%	100.0%	100.0%	100.0%	100.0%

Mortality

For purposes of the BIM, mortality is assessed at the end of each year based on the type of treatment received. Eculizumab patients are assumed to have the background mortality rate, considering that only one patient died over three years of extension data collected from the two main eculizumab clinical trials (C08-002 and C08-003). Specifically, the 1 death was over 352.2 patient years, or 0.28% mortality rate. Accordingly, we assume a background annual probability of death for a 28-year old patient based on the Office of National Statistics annual mortality rates.[6]

For patients receiving SOC prior to the availability of eculizumab, we assume a mortality rate based Coppo et al., 2010, which found mortality of 11.7% at an average follow-up of 17.8 months in 214 patients, and which equates to about 8% mortality per year. (Please see Section 12.8, subsection "SOC: The transitions between CKD states" for a discussion of Coppo et al., 2010.)

Patients on Eculizumab

In the BIM, patients are followed according to each year that they initiate therapy so that induction and maintenance doses can be separately measured. Treatment

[6] Office of National Statistics data, annual mortality, http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables#tab-data-tables. Last accessed August 20, 2013.

initiation is assumed to occur in the middle of a year, thus new patients receive one-half of a year's worth of doses. Maintenance patients receive a full year of doses. For 2013, data have been forecast reflecting anticipated full year eculizumab-treated patients based on access criteria applied by NHS England between April and September 2013. Thereafter, uptake is based on the assumption that the recommendations of the Clinical Priorities Advisory Group (CPAG) are formally ratified by the Directly Commissioned Services Group (DCSG) whereby NHS England will commission eculizumab for new patients with aHUS (defined to include those with a functioning kidney), and for existing patients who are on dialysis and are suitable for a kidney transplant. A commissioning for evaluation scheme will be developed for patients who are not suitable for transplant (Table D25).

Table D25: Estimated Number of Patients Treated with Eculizumab in England over a Five-Year Period

	Year 1 (2013)	**Year 2 (2014)**	**Year 3 (2015)**	**Year 4 (2016)**	**Year 5 (2017)**
Treatable aHUS population	296.3	308.6	324.1	342.8	362.3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]					[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: As described above, exact calculations are presented with zero decimal places showing.

The expected numbers of patients treated with eculizumab are multiplied by the expected number of vials per patient to reach an estimate of the total eculizumab drug cost over the five-year forecast period (described further below). It should be noted that the vial consumption is based on a compliance rate of 100% in all treated patients, which is likely an over-estimate of the actual vial consumption over time.

Dosing and Expected Vials Consumed per Patient

Per the European Medicines Agency (EMA)-approved label, the aHUS dosing regimen for adult patients (≥18 years of age) consists of a four-week initial phase followed by an on-going maintenance phase:

- Initial phase: 900 mg of eculizumab via an intravenous infusion every week for the first four weeks.
- Maintenance phase: 1,200 mg of eculizumab administered via an intravenous infusion for the fifth week, followed by 1,200 mg of eculizumab administered via an intravenous infusion every 14 ± 2 days.

In paediatric aHUS patients (aged less than 12 years), and adolescent patients (aged 12 years to under 18 years), the eculizumab dosing regimen is outlined in Table D26

below. In the associated Excel spreadsheet that contains the BIM (Appendix 8), the worksheet labelled “Dose Table” contains a weekly accounting of all vials in the induction (initial) and maintenance phases for patients on eculizumab therapy during a year of treatment.

Table D26: Dosing Schedule by Patient Weight

Patient Body Weight	Initial Phase	Maintenance Phase
5 - <10 kg	300 mg weekly x 1	300 mg at week 2; then 300 mg every 3 weeks
10 - <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every 2 weeks
20 - <30 kg	600 mg weekly x 2	600 mg at week 3; then 600 mg every 2 weeks
30 - <40 kg	600 mg weekly x 2	900 mg at week 3; then 900 mg every 2 weeks
≥40kg	900 mg weekly x 4	1,200 mg at week 5; then 1200 mg every 2 weeks

Table D27 below provides estimates of the total vials consumed per year for induction (initial) and maintenance aHUS patients by different patient weights. As noted above, new patients are assumed to initiate therapy mid-year in the model so these patients receive one-half of a full year’s worth of induction therapy. Maintenance patients receive a full year of maintenance vials.

Table D27 also includes the “Patient Population Weight Distribution,” which represents the estimated body weight distribution for persons diagnosed with aHUS based on information Alexion has collected globally. In the baseline year of the model, 60% of patients are assumed to receive adult dosing, with the remainder uniformly distributed over the other four paediatric dosing schedules. In the next four years of the model, 70% of patients are assumed to receive adult dosing, with the remainder uniformly distributed over the other four paediatric dosing schedules. The model uses a five-year average of these weight distribution assumptions in its estimated dosing calculation. Please note that the patient weight distribution is entered into cells C31 to G35 on the “Parameters” worksheet in the attached BIM spreadsheet (Appendix 8).

Table D27: Eculizumab Vial Usage Rate – Estimates of Vials Consumed

	Pt Population Wt Distribution (Average Yr 1 to Yr 5)	New Pt. Doses (1/2 year)	Maint. Pt. Doses (full year)
Paediatric patients weighing 5 – 10 kg	[redacted]	10	18
Paediatric patients weighing 10 - <20 kg	[redacted]	15	26
Paediatric patients weighing 20 - <30 kg	[redacted]	28	52
Paediatric patients weighing 30 - <40 kg	[redacted]	40	78
Adult dosing weight (> 40 kg)	[redacted]	56	104

	Pt Population Wt Distribution (Average Yr 1 to Yr 5)	New Pt. Doses (1/2 year)	Maint. Pt. Doses (full year)
Annuals vials consumed by a patient in a patient group (based on weighted average of the five different weight categories in Table C above)	[redacted]	46 vials	85 vials

Multiplying the expected number of doses for new and maintenance patients by the weight distribution yields the expected number of vials consumed for a patient in each of the groups in one year, which is 46 and 85 vials, respectively. (See row 47 of worksheet labelled "Parameters.").

Expected vials per patient are then multiplied by the number of patients in each group expected to receive eculizumab (Table D28).

Table D28: Eculizumab Vial Usage Rate by Estimated Numbers of Patients

Number of vials	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost of Eculizumab

The ex-factory price for eculizumab in the UK is £3,150 per vial (see cell C26 in the worksheet labelled "Parameters"). Based on the vial estimates in Table D33 above, and the per vial ex-factory price of eculizumab, the estimated annual total budget costs are provided in Table D29 below.

Table D29: Estimated Total Population Cost over a Five-Year Period for Eculizumab in aHUS Patients in England

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Other Healthcare Costs

Patients receiving eculizumab are expected to use other non-biologic healthcare resources, which must be accounted for in the BIM. This costing appears in the sheet "Direct Med Costs". Annual costs are included for eculizumab-treated patients in accordance with their average distribution over the first five years in the "alive health states" in the cost-effectiveness model included as part of this submission for those treated with eculizumab including CKD 0-1-2, CKD 3-4, ESRF, and kidney transplant. The costs per health state are multiplied by the distribution to get a weighted average cost.

SOC Costs

SOC costs must also be calculated for the "Eculizumab Available Scenario," considering that some proportion of patients will receive SOC based on Table D29 above entitled "Estimated Market Uptake of Eculizumab in aHUS". The costs of SOC include plasma exchange, CKD health state and ESRF costs. Similar to the eculizumab direct medical costing described above, annual costs are included for SOC-treated patients in accordance with their average distribution over the first five years in the alive health states in the cost-effectiveness model for those treated with SOC including CKD 0-1-2, CKD 3-4, ESRF, and kidney transplant. The costs per health state are multiplied by the distribution to get a weighted average cost. Plasma costs are added for patients in the CKD 0-1-2 and CKD 3-4 states. The derivation and sourcing of these costs are described in detail in Section 12.3.7 of this submission.

SOC Scenario

The SOC scenario is calculated in an identical fashion to the eculizumab scenario (see "No Ecu Scenario" worksheet in Appendix 8), but using the SOC/eculizumab market distribution found in the bottom two rows in Table D29 above.

13.4 Describe any estimates of resource savings associated with the use of the technology.

The model estimates that conditional on being alive, eculizumab reduces non-biologic direct medical costs by 80%. These costs are based on eculizumab treated

patients spending less time in more costly states like ESRF, transplant, and CKD 3a-4, and more time in CKD 0-2.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Per our earlier comments, major direct medical costs are excluded, including those not related to renal morbidity. These costs, for resource use associated with stroke, cardiac arrest, deep vein thrombosis for example, can be relatively high. Also, indirect costs and benefits are excluded; see the limitations in this section.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

As we note in more detail in the limitations section, societal indirect costs and benefits are excluded.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Net Budget Impact

The net budget impact for eculizumab in aHUS in England is provided in Table D30 below. Due to the ultra-rare nature of aHUS, and therefore the limited number of patients who will benefit from this life-saving therapy, eculizumab is expected to have an overall limited five-year budget impact in England of the following:

[redacted]

Table D30: Net budget impact calculation

COSTS	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Scenario where eculizumab available					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
other direct medical costs	£194,571	£405,336	£638,437	£750,363	£872,424
SOC costs	£5,460,838	£4,684,307	£3,864,755	£3,716,426	£3,535,340
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario where eculizumab not available	£6,424,516	£6,614,841	£6,795,528	£6,967,395	£7,131,198
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs of remaining alive longer with eculizumab

It is important to note that the BIM indicates that the direct medical cost expenditure to the NHS is between £8 and £10 million over the 5-year budget window. That is, if eculizumab had the same mortality rate as SOC, the NHS would save between £8 and £10 million over the period calculated in the BIM. Excluded from this analysis are the health benefits accrued to patients on eculizumab, as well as any costs aside from direct medical expenses. The incomes and other goods produced by these patients who would have died, as well as the incomes and other goods produced by these patients and their caretakers who would become more functional, healthier members of society, but do not because of eculizumab, are excluded from the BIM. Given the particular circumstances of the aHUS patient population, namely the difficulties in patients with an ultra-rare disease to access new medicines, we recommend that the NHS recognize the flaws in the BIM method when reviewing this submission.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

As explained in Section 13.7 above, the budget impact of the eculizumab scenario is likely overstated. It also is expected that availability of eculizumab for the treatment of aHUS would significantly reduce the morbidity of patients with the disease. However, health utility is excluded from this BIM. As seen in the eculizumab aHUS clinical trials (Legendre et al 2013), and the cost-effectiveness model included in Section 12 of this submission, a large health utility increase is attributed to eculizumab vs. SOC. Such effects, even monetised versions of them, are excluded from BIM, which biases the cost estimate against eculizumab when considered in a societal context. Moreover, due to the abbreviated time horizon of the BIM, the total life years lost by SOC are not included from a budget perspective. Indirect costs would likely be reduced by eculizumab given its substantial improvement in patients' quality of life, but there are no published studies which quantify these effects in a form that could be included in the BIM. Collectively, these effects are not included in the current analysis, and the budget impact of the eculizumab scenario is likely overstated as a result.

Section E – Impact of the technology beyond direct health benefits and on the delivery of the specialised service

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.
Section 15 is aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

The economic costs of sickness absence and worklessness associated with working age ill-health are over £100 billion a year in the UK–greater than the current annual budget for the National Health Service (NHS).(DoH 2008) In a condition as severe as atypical Haemolytic Uraemic Syndrome (aHUS), is it is therefore likely that considerable per-patient cost is associated with the disease, beyond that incurred by the NHS and PSS. Accordingly, it is expected that by significantly reducing patient morbidity, eculizumab has the potential to reduce the wider societal burden of the disease.

The impact of aHUS on patients and carers is described in Section 7. The current section, Section 14, attempts to quantify this impact and estimate cost savings that might be possible with eculizumab. The following economic domains are considered:

- Societal Costs
    - Productivity loss
    - Foregone tax revenue
    - Government benefits;

- Out of pocket expenditure for patients and carers
    - Transportation
    - Housing
    - Other costs; and

- Other carer costs.

In Tables E1, E2, E3 below, the total cost of each of these elements is calculated per aHUS patient (and for all English aHUS patients, using the number of patients predicted in Section 13), and the savings/improvements associated with eculizumab are estimated. Assumptions used in the calculations are discussed in the sub-sections below.

No data have been collected on the direct effect of eculizumab on these economic domains; therefore, cost savings have been estimated for two scenarios assuming an eculizumab effect size on indirect costs of 75% or 25%.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Eculizumab savings to government bodies (beyond the NHS) and to the wider economy are estimated in Table E1.

Patient lost productivity was estimated based upon the excess unemployment amongst adult aHUS patients. This was estimated by comparing the proportion of adult aHUS patients who were out of work (but not retired) in the UK aHUS patient survey (Section 7) with the current UK unemployment rate. The societal cost of this excess unemployment was calculated by applying this excess unemployment rate to the median UK salary.(ONS, 2012)

A similar calculation was undertaken for carers, based upon findings from the UK aHUS patient survey that suggested that 54% of patients had an informal carer and carers, on average, lost 18 hours of paid work a week due to their carer responsibilities. It has also been found that individuals who leave the work force to become carers have significantly reduced incomes at the point of re-joining the workforce, with salaries of half of those of the average worker.

Both aHUS patients and carers can receive government disability-related benefit payments as a result of the aHUS health impact on the patient. It was assumed that 25% of aHUS patients would be in receipt of such benefits. The average potential disability benefit that a high-medium disability patient is eligible for has been found to be £235 per week.(Wood et al 2010) Sixty-one percent of carers in the UK also receive Carer's Allowance which is worth £59.75 per week.(Carers UK, 2007)

Lost tax revenue due to aHUS was estimated based upon the productivity impairment to patients and carers described above. The average percentage of salaries that are paid to the government in tax is 17.8%.(LSE, 2013)

Table E1: Estimated government (non-NHS) and societal costs associated with aHUS and potential savings with eculizumab

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Patient lost productivity	40% of adult aHUS patients were out of work in UK aHUS patient survey (Section 7). 23% of out of work adult aHUS patients were retired. Therefore estimate that 27% (0.4 x 0.67) of all adult aHUS patients are out of work vs. 7% for general population. Assume 20% excess unemployment rate. Assume adults represent 50% of total population	Average median UK annual earnings £26,500 (ONS 2012)	0.2 x 0.5 x £26,500 = £2,650	£784,400	£588,300	£196,100
Carer lost productivity (current carers)	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) Carers on average lost 18 hours of paid work per week, which represents 46% of an average 39 hour working week (ONS 2012)	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.54 x 0.82 x 0.46 = £5,397	£1,597,729	£1,198,297	£399,432
Carer lost productivity (ex-carers)	The household income of ex-carers is approximately half of household income of general population (McLaughlin and Ritchie 1994). Assumes ex-carers = 25% current patients (82% were informal carers (UK aHUS patient survey))	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.5 x 0.25 x 0.82 = £2,716	£804,010	£603,008	£201,003

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Patient receipt of government benefits	Assume 25% of aHUS patients receives benefits	High-medium need total weekly benefits = £235 (Wood 2010)	0.25 x £235 x 52 = £3,055	£904,280	£678,210	£226,070
Carer receipt of government benefits	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) 61% of carers receive Carer's Allowance (Carers UK, 2007)	Carer's allowance = £59.75 per week (UK Government 2013)	0.54 x 0.82 x 0.61 x £59.75 x 52 = £839	£248,411	£186,308	£62,102
Lost tax revenues for patients	20% excess employment rate for patients (see above) Average percentage of income that goes on tax = 17.8% (LSE 2013)	Average median UK annual earnings £26,500 (ONS 2012)	0.2 x £26,500 x 0.178 = £943	£279,246	£209,434	£69,812
Lost tax revenues for carers	54% of patients have a carer (82% were informal carers) who lose 18 hours work per week on average (see above) which represents 46% of an average 39 hour working week (ONS 2012) Average percentage of income that goes on tax = 17.8% (LSE 2013)	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.54 x 0.82 x 0.46 x 0.178 = £960	£284,396	£213,297	£71,098

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Patient out-of-pocket costs and eculizumab savings to patients are estimated in Table E2 below.

Transport costs range widely, with patients spending between £90 and £780 a year on travel.(UK aHUS patient survey 2013; Roderick 2005) On average, patients with aHUS have to spend four hours travelling each week for activities associated with their aHUS, such as hospital visits.(UK aHUS patient survey 2013)

The predominant costs in terms of household expenses are the adaptations required for home dialysis; for the estimated 31% of patients on home dialysis, this amounts to £1,291 annually.(NICE TA52, Final Appraisal Determination)

In circumstances whereby a patient moves into a carer's home, the associated opportunity cost of the accommodation (costed in terms of the opportunity to earn a market rent) is estimated at approximately £4,834 per year. This is based on the assumption that 10% of informal carers take in aHUS patients (in the absence of available data).

Forty percent of patients stated that they had had to move as a result of their (or their child's) disease. Reasons provided for moving include: being closer to a specialist centre, closer to a relative or carer, or being in a more suitable type of accommodation.(UK aHUS patient survey 2013) The average cost associated with moving home in the UK is £8,922.

Table E2: Estimated out of pocket patient and carer costs associated with aHUS and potential savings with eculizumab

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Transport	aHUS-related travel ranges from twice-weekly to once a month, patients spend approximately 4 hours each week (UK aHUS patient survey)	Average of £7.50 per trip (based on range of £1–15 per trip reported by UK patients on dialysis (Roderick 2005)	Up to £7.50 x 2 x 52 = £780	Up to £230,880	Up to £173,160	Up to £57,720
Direct financial expenditure on **goods and services**, such as additional household expenses or extra lighting/heating (Glendinning 1992 (as cited in Pickard 2004); Netten 1993).	According to reference costs 2011/12, 31% are on home dialysis. 34% of patients are on dialysis (UK aHUS patient survey)	Average cost of home conversion for home dialysis is £1,291** per year over 4 years (NICE TA48).		£1,291 x 0.31 x 0.34 = £136	£40,277	£30,208
Accommodation costs: where the cared-for person moves into the carer's house, the cost of the room can be costed in terms of the opportunity to earn a market rent (Netten 1993).	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) Assume 10% carers take in the cared-for person	Average accommodation cost is £4,834 (National Union of Students, 2012/13)		£4,834 x 0.54 x 0.82 x 0.1 = £214	£63,359	£47,518

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Requirement to move house, e.g. due to mains water supply needed for haemodialysis	22% of families had to move house due to aHUS (UK aHUS patient survey)	Average cost of moving home is £8,922 in the UK (Bank of Scotland 2012)	£8,922 x 0.22 = £1,963	£581,048	£435,786	£145,262

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

Carer costs and associated eculizumab savings are estimated in Table E3 below.

In the UK aHUS patient survey, carers estimated they spent on average 44 hours looking after an aHUS patient. This was based upon a sample of nine respondents who provided an estimate of the number of hours they spend caring. The average hourly cost for a formal carer is £14.50 per hour (NHS Information Centre) so the potential value of the average aHUS carer is £33,176 per year.

As well as the value of the care provided by carers, there are other costs that are considered in Table E3, such as the economic burden on carers as a result of the stress incurred. Informal carers take on a wide range of responsibilities, such as (Jackson 2013):

- grooming, dressing and eating (encompassing personal care), communication;
- supervision;
- transport;
- administration – dealing with agencies, appointments, financial and legal affairs;
- therapy and leisure – encouraging exercises, reading and planning outside activities; and
- psychosocial support – providing reassurance, motivation and problem solving.

Given the extent of the support provided, the physical and mental health and wellbeing of carers is often impacted. Typical health issues experienced by carers include mild-moderate depression, stress-related angina, and chronic lower back pain.(Access Economics 2010) Carers have a higher incidence of mental illness than the general population; clinical studies have shown increased rates of depression among caregivers, compared to control populations.(Spector and Tampi, 2005, cited in Access Economics 2010)

In a study of the effectiveness and cost effectiveness of support and services to informal carers of older people, the average healthcare costs of carers of older patients with neurological conditions was £1,424.(LTNC 2011) Assuming carers of aHUS patients incur about one-third of this amount (due to the younger mean age), this represents £475 per year spent in healthcare costs.

The average cost to the carer was estimated in 1990 to be £31.42 a week. This cost includes: direct financial expenditure on goods and services, forgone non-waged time, forgone waged time, forgone career prospects, and forgone accommodation costs. It was also considered close in value to the 'social opportunity cost'.(Netten 1990) The true current cost is likely to be much higher, given cost inflation since 1990.

In the UK aHUS patient survey outlined in Section 7, 44% of carers reported feeling stressed "a lot of the time", or "always". This finding corresponds closely to that reported by the PSSRU, which stated that 47% of carers are stressed.(Picard 2004) Furthermore, the report found that carers who were stressed had higher costs of

social services than carers who were not stressed; the weighted average annual costs of social services were £876 per year for stressed/non-stressed carers.

Table E3: Carer costs

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual cost across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Value of informal care provided by carers	On average, carers in the UK aHUS survey spent 44 hours a week looking after a patient with aHUS. 54% of aHUS patients with carers and 82% of these are informal carers (aHUS patient Survey UK)	£14.50 per out of formal care (NHS Information Centre)	£14.5 x 44 x 52 x 0.54 x 0.82 = £14,690	£4,348,339	£3,261,254	£1,087,085
Mean **healthcare** service use **by carers** which includes GP, other doctor, nurses, therapist, psychologist, counsellor, dentist, in-patient care, and support groups	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) During the previous year, in-patient care had been received by 1 in 14 carers of older patients with neurological conditions, with two thirds having seen their GP. Half had seen a dentist and a quarter had seen another doctor and/or a practice nurse. About one in 17 had seen one or more other health professionals; namely a therapist, psychologist or counsellor (LTNC 2011).	Average cost for carers of older patients with neurological conditions are £1,424 (LTNC 2011) Given younger mean age of aHUS patients (29 yrs), this figure is divided by 3		£1,424 / 3 x 0.54 x 0.82 = £210	£62,214	£46,660

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual cost across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Social opportunity cost – carer, includes direct financial expenditure on goods and services; forgone non-waged time; forgone waged time; forgone career prospects; and forgone accommodation costs (Netten 1990).	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey)	Average cost to the carer of £31.42 a week overall (Netten 1990)	£31.42 x 52 x 0.54 x 0.82 = £723 per year	£214,145	£160,609	£53,536

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or on-going, please provide details.

Eculizumab is the only approved and targeted therapy to treat aHUS patients, a chronic and progressive complement mediated disease. Recent clinical advances in aHUS prior to the registration and recent eculizumab trials clinical trials have focused on the identification of genetic mutations in aHUS patients that have suggested a central role for uncontrolled complement activity. Eculizumab has provided a proof of concept for the role of chronic complement activation as the central mechanism for the morbidity and mortality in aHUS. It has been reported that 33% to 40% of aHUS will reach ESRF or die following the first clinical presentation of TMA. Blocking complement C5 with eculizumab has eliminated the progression to ESRF and has significantly reduced the risk of long-term dialysis leading to a significantly reduced mortality associated with aHUS. Long-term treatment with eculizumab has shown improvement in renal function in situations where investigators have assumed permanent damage to the kidney, highlight further investigation to the chronic inflammatory and coagulation activity that is occurring in the absence of overt platelet consumption.

There continues to be on going interest to further identify potential bio markers related to inflammation or renal damage to demonstrate on-going disease, to better manage patients instead of relying on overt platelet consumption previous utilized by clinicians. Based on the survival of kidney and life extension as well as significant improved quality of life (and therefore indirect productive societal activity) these results have enlightened investigators to reconsider what should be the expected and achievable outcome in aHUS patients.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

In terms of innovation to the NHS specifically, the aetiology of aHUS was unknown 15 years ago. In 1998, the Newcastle group led by Professor Tim Goodship was the first to identify a mutation in the gene encoding the complement regulator factor H (Warwicker et al, Kidney Int. 1998). Since then, a series of studies have established that approximately 50-70% of aHUS patients have either an inherited or acquired abnormality of complement that is associated with over-activity of the complement system.(Noris and Remuzzi, 2009; Noris et al, 2010; Fremeaux-Bacchi et al, 2013) These findings provided the logic for the recent clinical trials of eculizumab to inhibit complement-mediated TMA in aHUS.

Establishing the routine use of eculizumab for the management of aHUS within England will maintain and enhance the international reputation that the UK has in the field of aHUS. The Renal Association and the British Association for Paediatric Nephrology have developed an integrated strategy for patients with rare kidney diseases. The three key aims of the strategy are to develop disease-specific working groups, develop care pathways, and develop a UK Registry for Rare Kidney Diseases (RaDaR). The proposed commissioning of eculizumab and potential development of a service based on centre/s of expertise for aHUS will have an impact at each of these levels. Kidney Research UK has recently issued a funding call for new rare disease working groups and has received an application for the establishment of such a group for aHUS on behalf of all interested parties within the

UK. The first aim of the group is to develop a registry of patients with aHUS (aHUS RaDaR). With NHS Kidney Care, care pathways are also being developed for aHUS which will become an integral part of the service.

While the Newcastle group has been highly successful in identifying novel inherited and acquired factors that are associated with aHUS, the lack of an effective patient registry has meant that full characterisation of the natural history of the disease in the UK has been lacking as has the examination of genotype-phenotype associations. The proposed aHUS national service will thus enable the establishment of a unique resource for clinical research and further innovation. It is anticipated that the registry established will link with the Alexion global registry to avoid duplication of data entry.

Outside of aHUS specifically, a number of researchers are looking at the potential for complement inhibition to play a role in the management of a range of disorders characterised by over-activation of the complement system. In addition, Complement UK, an academic and research organisation with a specific interest in complement related disorders is actively looking at the role of complement inhibition. A Complement UK symposium and training course to take place in October 2013 will have a specific purpose to understand the role of complement in pathological and homeostatic conditions, to foster research collaboration and provide an overview of the current level of expertise within the UK.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

Alexion is sponsoring an international aHUS registry that will capture and continue to follow aHUS patients irrespective of treatment status. The objective of the registry is an observational study to better characterize the natural history of the disease in patients not treated with eculizumab and how eculizumab will impact the disease progression. Measures of mortality, progressive renal function, use of PE/PI, better categorization of non-renal TMA, and organ damage and mortality with or without the use of eculizumab treatment will be key outputs of the registry. The registry itself will have oversight from an independent committee comprising international physicians who will ensure appropriate utilisation of data, data searching and resultant publications to support on-going development of longitudinal knowledge of the disease and impact of treatment.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Clinical effectiveness will be reviewed as part of the on-going long-term follow-up study of patients previously included in eculizumab clinical trials as described in Section 9.4 and via the Registry as described in Section 14.7.

15 Impact of the technology on delivery of the specialised service

15.1 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

Eculizumab is simple to administer via intravenous infusion and is generally well-tolerated. It is therefore suitable for administration at appropriate centres throughout England and should be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders.

Due to the urgency of treatment, eculizumab will be initiated in local centres with support from a centre of expertise. No additional staffing requirements will be needed in local centres where aHUS patients may present. It is envisaged that most patients will transition to home care, which will be funded by Alexion, and offered to all aHUS patients receiving eculizumab in the UK. On-going follow-up will be provided by the expert centre working in collaboration with the local centre.

aHUS is an ultra-orphan disease, and expertise in the field is very limited owing to the low number of patients presenting annually. Professor Tim Goodship is an adult nephrologist with an international reputation in the field of aHUS based in Newcastle. His research group was the first to identify that mutations in complement regulators led to the development of the disease and subsequently many of the landmark papers in the field have emanated from his laboratory. Currently, Professor Goodship devotes the majority of his time supporting local centres in the UK and provides expert advice on diagnosis and management of aHUS cases. Professor Goodship is supported by his colleagues, Professor Neil Sheerin, who is an expert in renal transplantation and complement and Dr. David Kavanagh, who has recently been awarded a Wellcome Trust Intermediate Clinical Fellowship for a project titled "The convergence of complement and coagulation in atypical haemolytic uraemic syndrome".

The paediatric centre of expertise, also based in Newcastle, is currently led by Dr. Sally Johnson, a paediatric nephrologist with considerable experience in the management of aHUS in children. Dr Johnson works closely with the adult team to provide particular support and advice to paediatric renal and haematology colleagues across the UK.

15.2 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Infrastructure requirements are limited to the additional resource requirements within centre/s of expertise designated by NHS England to run the national aHUS service, whereby such centres would need full-time equivalent (FTE) resource to ensure adequate and immediate support of local centres on a constant basis (24 hours a day, 7 days a week).

No additional infrastructure will be required in local centres where aHUS patients may present.

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*References on order will be provided separately

17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Clinical evidence searches included:

- A search of the published literature (EMBASE, MEDLINE, Cochrane Database)
- A search of registers of randomized trials (NIH clinicaltrials.gov and Cochrane Central Register of Controlled Trials)
- Manual checking of reference lists of all relevant articles

17.1.2 The date on which the search was conducted.

The clinical evidence search was conducted 4 July, 2013.

17.1.3 The date span of the search.

1947 to 4 July 2013.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A comprehensive search was conducted to update and identify all studies on the clinical effectiveness of eculizumab and any adverse events associated the treatment of patients with aHUS.

Three strategic search approaches were used:

- A search of the published literature (EMBASE and MEDLINE, Cochrane database)
- A search of registers of randomized trials (NIH
- Manual checking of reference lists of all relevant articles

Before conducting the literature searches, entry criteria were defined for the inclusion and exclusion of papers. To be included, a reference had to report a clinical trial that met all the following criteria:

- A randomization procedure in the trial design
- Comparison of eculizumab versus supportive care, or alternatively was a placebo controlled eculizumab trial
- Participant characteristics consistent with aHUS.

The term 'atypical' was first used to describe non-diarrhoeal associated HUS as long ago as 1965. Haemolytic Uraemic Syndrome (HUS) is characterized by a combination of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. Since then, aHUS has been described as non-diarrhoeal HUS and non-shiga-toxin HUS (non-STEC HUS) but increasingly over the past decade, aHUS has become recognised as a disease process readily differentiated from HUS. For this reason, searching the literature for appropriate trials required a complex process. There are no reliable terms that apply to the majority of the literature on aHUS. Terminology that surrounds and sometimes refers to the disease that is aHUS includes: thrombotic microangiopathy (TMA), thrombotic thrombocytopaenic purpura (TTP), ADAMTS13, complement mutation, non-STEC-HUS and non-diarrhoeal HUS. This resulted in a relatively large number of publications (over 1000) which needed to be assessed using either abstract or full text. Hand searching reference lists of important publications was necessary in order to identify relevant publications and to prevent overlap of study populations under different authors.

The following primary selection criteria were used:

- Children and adults with atypical haemolytic uraemic syndrome (aHUS)
- Patients with typical or acquired haemolytic uraemic syndrome or without atypical haemolytic uraemic syndrome were excluded from the assessment.

Secondary journal level search criteria included requirements that:

- The initial selection include human, English-language only
- The highest level of available evidence to be included
- The earliest publication date was 2012 due to the same search being conducted for the 2012 PBAC submission.

The following search terms were used to identify relevant clinical evidence:

1 (atypical haemolytic uremic syndrome or atypical HUS or aHUS or non-diarrheal HUS or non stx HUS).mp. [mp=title, abstract, subject headings,

heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2 limit 1 to (human and english language and yr="2000 -Current")
3 (complement and allotransplantation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4 limit 3 to (human and english language and yr="2000 -Current")
5 *complement component C5/
6 limit 5 to (human and english language and yr="2000 -Current")
7 (haemolysis and complement).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8 limit 7 to (human and english language and yr="2000 -Current")
9 thrombotic microangiopathy.mp.
10 limit 9 to (human and english language and yr="2000 -Current")
11 2 or 4 or 6 or 8 or 10
12 limit 11 to (human and english language)
13 randomized controlled trial/
14 limit 12 to (human and english language and yr="2000 -Current")
15 13 and 14

Due to the difficulty in identifying a reliable search strategy, and the lack of high level evidence in the form of randomised controlled trials, the term 'trial' was extended to include case series, retrospective trials, registries, cohort and case studies.

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Company databases were searched for relevant clinical trial protocols and clinical study reports.

17.1.6 The inclusion and exclusion criteria.

Primary inclusion criteria: children and adults with atypical haemolytic uraemic syndrome (aHUS) (Table E4)

Table E4: Summary of search output exclusions (RCT Search)

	Citations retrieved		
Eculizumab Search	**EMBASE including Medline**	**Cochrane CCTR**	**NIH**
Number of citations retrieved by search	57	4	0
Identical Duplicate	1		
Number Reviewed	56	4	0
Number of citations excluded after title/abstract review:			
A: not a randomized trial	21		
B: randomized trial does not include the proposed drug and the main comparator in separate arms	1		
C: characteristics of the recruited participants do not overlap with the main indication	34	4	

	Citations retrieved		
Eculizumab Search	**EMBASE including Medline**	**Cochrane CCTR**	**NIH**
Consolidated number of citations of direct randomized trials	0	0	0
Number of multiple (additional) citations of direct randomized trials identified	0	0	0
Number of citations of direct randomized trials	0	0	0

17.1.7 The data abstraction strategy.

Full citation details and abstracts of all studies identified in the searches were downloaded and reviewed. If a paper could not be excluded on the basis of the information in the title or abstract, the full paper was retrieved before any decision was made. Duplicate citations were removed and all relevant papers retrieved. The identified relevant citations were then analysed for inclusion as described in 17.1.6.

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The clinical evidence search as described in 17.1 was utilized to identify relevant studies including safety analysis and AE data. Alexion-supplied Product Update Safety Reports were also reviewed for relevant data.

17.2.2 The date on which the search was conducted.

4 July 2013 for external sources; 6 September 2013 for internal sources.

17.2.3 The date span of the search.

1947 – 4 July 2013 for database searches

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Adverse events were identified using the search strategy identified in 17.2.4.

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches for AEs were included in additional searches for clinical evidence, as described in 17.1.5.

17.2.6 The inclusion and exclusion criteria.

Inclusion/exclusion criteria were as described for clinical evidence in section 17.1.6.

17.2.7 The data abstraction strategy.

Data abstraction for AEs were as described for clinical evidence in section 17.1.7

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

A systematic review was undertaken to support the creation of the model described in Section 12. The literature review was specific to aHUS. Given the very small body of published evidence in this disease, a broad search was undertaken to obtain the following information:

- Information on resource use and costs in aHUS
- Economic studies in aHUS
- Quality of life data in aHUS

Thus the systematic review described in this section applies to Appendices 3 and 4, as well as describing the methods and results for the systematic review of Quality of Life data.

Search Strategy

The following electronic databases were searched:

- PubMed
- EMBASE
- Web of Knowledge
- Scopus
- CINAHL
- 'Biological Abstracts'
- EconLit
- NHS EED
- NHS HTA

Selection Criteria

The following primary selection criteria were used:

- Children and adults with atypical haemolytic uraemic syndrome with variations to account for differences in spelling (see Section 17.3.4 below).

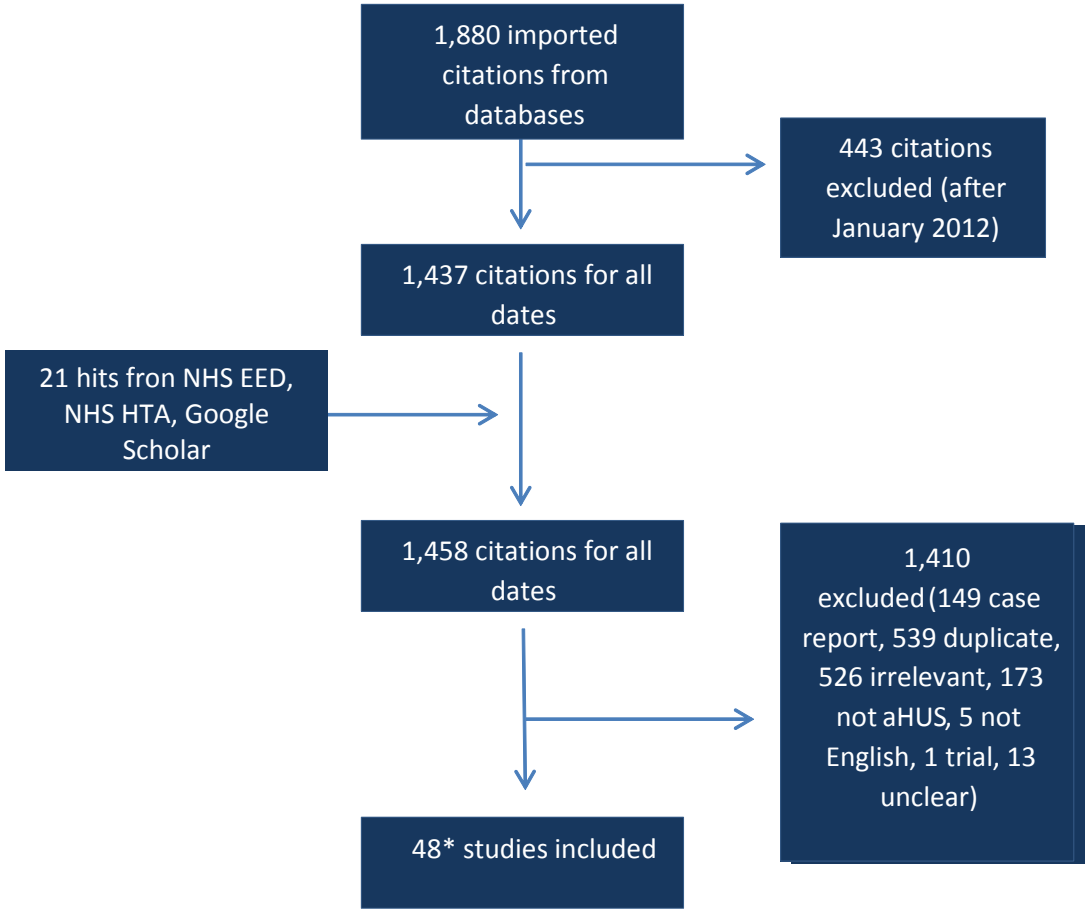
The following exclusion criteria were used:

- Non-English language
- Studies in patients other than with atypical haemolytic uraemic syndrome
- Reviews
- Studies in animals and genetic/protein studies
- Studies without relevant outcomes reported, i.e. studies not reporting any of the following:
  - death
  - adverse events/effects
  - HRQL or utility
  - change in platelet count
  - change in haemoglobin count
  - need for dialysis
  - need for kidney transplantation
  - estimated Glomerular Filtration Rate (eGFR).
  - change in TMA
  - cost or resource use information
  - economic evaluations

Data Abstraction Strategy

Retrieved citations were first reviewed in abstract form, with citations clearly not meeting the inclusion criteria excluded at this stage. The full text versions of the included citations were then ordered, and reviewed again with the inclusion/exclusion criteria. Data from these papers were extracted into an extraction grid prepared in Microsoft Excel. All stages were performed by one or two reviewers, with queries resolved by another independent reviewer.

Figure E1: Results: Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) Flow Diagram



** 20 of the included papers were extracted on the basis of the abstract alone, as full-text versions were not available (published as conference abstracts, or the pertinent issue of the source journal did not contain the full text papers due to incorrect indexing in the databases)*

17.3.2 The date on which the search was conducted.

The search was conducted on 19 July 2013.

17.3.3 The date span of the search.

The searched spanned from inception to 19 July 2013.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The MEDLINE search strategy used is as follows, with adaptations to the search formulation made according to the specifications of each database. No automated restrictions according to language or date were applied.

1 atypical h?emolytic ur?emic syndrome$.tw.
2 ahus.tw.
3 1 or 2

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

17.4 Appendix 4: Resource identification, measurement and valuation

For answers to questions 17.4.1 to 17.4.7, please see Section 17.3, which describes the combined systematic review performed including resource use, quality of life, and economic data.

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

See Section 17.3.

17.4.2 The date on which the search was conducted.

See Section 17.3.

17.4.3 The date span of the search.

See Section 17.3.

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 17.3.

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 17.3.

17.4.6 The inclusion and exclusion criteria.

See Section 17.3.

17.4.7 The data abstraction strategy.

See Section 17.3.

No studies reporting economic or cost data were retrieved from the literature review. Only one study reported quality of life information (Table E5 below).

Table E5: Summary of studies reporting quality of life information

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Quality of Life Data
Eculizumab (ECU) significantly improves Health-Related Quality of Life (HRQoL) in patients with atypical haemolytic uremic syndrome (aHUS)	Muus P;Licht C; Goodship THJ;Greenbaum L;Bedrosian CL; Loirat C;Legendre C;	2011	17 aHUS pts	Median age 28 yrs	NR	2 prospective, controlled, single-arm phase II trials of aHUS pts receiving ECU.	In both cohorts of distinct trial pts, ECU substantially improved HRQoL through Wk 26, and sustained this thereafter during long-term ECU therapy (table). In trial C08-002, improvements were seen as early as Day 7 (0.12, p=0.0346). Point estimate improvement (95% CI) in HRQoL from baseline to 1 yr was 0.32 (0.27-0.36) for C08-002 and 0.09 (0.05-0.14) for C08-003. On an individual pt basis, 87% and 73% of C08-002 and C08-003 pts, respectively, achieved a clinically meaningful change that represented a clinically important large or moderate improvement in HRQoL measures, respectively.
Terminal Complement Inhibitor Eculizumab in Atypical Haemolytic–Uremic Syndrome	Legendre C; Licht C;Muus P; Greenbaum L.A;Babu S; Bedrosian C;Bingham C;Cohen DJ;et al.	2013	37 aHUS patients	Median age 28 yrs	27 European and North American clinical sites	Thirty-seven patients with atypical haemolytic–uremic syndrome: 31 adults and 6 children.	Eculizumab was associated with a significant improvement in health-related quality of life. The EQ-5D scores range from 0 to 1. In Trial 1 the mean increase in the EQ-5D score at week 26 was 0.32 (95% CI, 0.24 to 0.39; P<0.001). In trial 2, the mean increase was 0.10 (95% CI, 0.05 to 0.15; P<0.001). The clinically meaningful threshold of 0.06 was exceeded in 87% of patients in trial 1 and in 73% of patients in trial 2 throughout the treatment period.

Table E6: Summary of studies reporting resource use information: dialysis

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Dialysis resources used							

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Prognostic value of renal pathological findings in children with atypical hemolytic uremic syndrome	Mehrazma M; Hooman N; Otukesh H	2011	29 children	NR	Iran	AHUS pts between 1992 and 2005 in Ali Asghar Children Hospital.	5 pts underwent dialysis
Plasma therapy for atypical haemolytic uraemic syndrome associated with heterozygous factor H mutations	Kim JJ;Goodship TH;Tizard J;Inward C;	2011	3 children	Mean age 10.6 months	UK	Patients with heterozygous CFH mutations associated with aHUS	All three required dialysis: peritoneal dialysis for patient 1 and haemodialysis for patients 2 and 3
Hemolytic-Uremic Syndrome in Uberlandia, MG, Brazil	Bonetti V;Mangia CM;Zuza JM;Barcelos MO;Fonseca MM;Nery SP;Carvalhaes JT;Andrade MC;	2011	27 children	Median age 14 months	Brazil	Children diagnosed with HUS from January 1, 1994 to January 31, 2004 in the pediatric nephrology department of the Hospital de Clinicas, Universidade Federal de Uberlandia, MG, Brazil	Dialysis was performed on 20 patients (74%)
Atypical hemolytic uremic syndrome in the Tunisian population	Leban N;Aloui S;Touati D;Lakhdhar R;Skhiri H;Lefranc G;Achour A;Elmay M;Lopez-Trascasa M;Sanchez-Corral P;Chibani J;Haj KA;	2011	4 adults	Mean age 36 years	Tunisia	Four cases of atypical HUS in adults admitted in the Nephrology Department of Fattouma Bourguiba Universitary Hospital in Monastir between 2000 and 2008	Patient 1: The patient remained on chronic dialysis (3 sessions per week)., patient 3: the patient is undergoing chronic hemodialysis and waiting for a kidney graft

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations	Fakhouri F;Roumenina L;Provot F;Sallee M;Caillard S;Couzi L;Essig M;Ribes D;Dragon-Durey MA;Bridoux F;Rondeau E;Fremeaux-Bacchi V;	2010	21 adults	Mean age 28 years	France	French cohort of adult patients with TMA	81% patients (17 of 21) required hemodialysis at the acute phase of the disease
Pulse cyclophosphamide therapy and clinical remission in atypical hemolytic uremic syndrome with anti-complement factor H autoantibodies	Boyer O;Balzamo E;Charbit M;Biebuyck-Gouge N;Salomon R;Dragon-Durey MA;Fremeaux-Bacchi V;Niaudet P;	2010	3 children	Mean age 5.8 years	NR	3 children with atypical hemolytic uremic syndrome associated with anti–complement factor H (CFH) autoantibodies	Patient 2: treated with peritoneal dialysis
Hemolytic-uremic syndrome in Switzerland: a nationwide surveillance 1997-2003	Schifferli A;von Vigier RO;Fontana M;Sparta G;Schmid H;Bianchetti MG;Rudin C;	2010	6 children with aHUS	Median age 21 months (for all the group not the aHUS pts)	Switzerland	National study through the Swiss Pediatric Surveillance Unit 114 HUS cases	1 patient with aHUS was treated with dialysis with a median duration of 14 days
Atypical Hemolytic Uremic Syndrome Associated With Complement Factor H Autoantibodies and CFHR1/CFHR3 Deficiency	Lee BH;Kwak SH;Il Shin J;Lee SH;Choi HJ;Kang HG;Ha IS;Lee JS;Dragon-Durey MA;Choi Y;Il Cheong H;	2009	3 children	Mean age 8.6 years at onset	NR	Three patients were clinically diagnosed as aHUS,	Patient 1 and 3: were on hemodialysis

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Long-term outcome of children previously on dialysis therapy for hemolytic uremic syndrome	Szczepaõska M;Szprynger K;Niwiõska-Faryna B;Muszewska E;	2008	19 aHUS children	Mean age of 46.3 ± 50.0 months for all the group of pts	Poland	HUS hospitalized patients at the Department and Clinics of Pediatrics in Zabrze of Silesian Medical University in Katowice from 1990 to 2006.	Peritoneal dialysis was applied as the principal method of renal replacement therapy in 33 children (76.7%) and hemodialysis in 9 children (23.3%).(for all group including aHUS pts)
Hemolytic uremic syndrome in Kuwaiti Arab children	Al-Eisa A;Al-Hajeri M;	2001	11 aHUS children	Mean age at presentation was 34.2±38.2 months in the D– HUS group	Kuwait	Twenty-five children with HUS diagnosed between January 1985 and January 2000 in the Pediatric Nephrology Unit at Mubarak Al-Kabeer Hospital	Dialysis was needed in 100% of patients with atypical HUS (P=0.05).The peritoneal route was used in all of them for a mean duration of 14 days in the D– HUS group
Heterogeneity of atypical haemolytic uraemic syndromes	Neuhaus TJ;Calonder S;Leumann EP;	1997	23 children	Median age 4.9 years	Switzerland	Clinical and laboratory features of 23 children with D−HUS	Seventeen patients (74%) were dialysed: 10 (including the two children who died) had temporary dialysis for 5–122 days (median 28 days) and seven (30%) subsequently required long term dialysis
Atypical hemolytic-uremic syndrome: a comparison with postdiarrheal disease	Siegler RL;Pavia AT;Hansen FL;Christofferson RD;Cook JB;	1996	22 children with aHUS	Median ages 3.5 years	USA, Utah	Residents of Utah or surrounding states and had been cared for at the University of Utah Health Sciences Center, or its close affiliate, Primary Children's Medical Center	Patients in the atypical disease group were less likely to need dialysis (21%)
Outcome and prognostic determinants in the hemolytic uremic syndrome of children	Tonshoff B;Sammet A;Sanden I;Mehls O;Waldherr R;Scharer K;	1994	21 aHUS children	Median 3.1 years	Germany	Children with HUS observed from 1971-1988 treated in University Children's Hospital in Heidelberg	Data for patients who died: peritoneal dialysis 2 pts and hemodialysis 4 pts with aHUS

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Eculizumab is effective in patients resistant to plasma exchange/infusion with atypical haemolytic uremic syndrome (AHUS)	Bedrosian C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Loirat C;Greenbaum L;Zimmerhaekl L;Legendre C;	2011	17 aHUS pts	15 of 17 pts group with median age 28 years	NR	26-week, controlled, open-label, single-arm trial, pts > 12 years were enroled with plasma-resistant aHUS	29% were on dialysis immediately prior to eculizumab. four of five pts became dialysis-free
Prophylactic plasmapheresis (PE) and eculizumab (EC) allow long term renal function preservation in FH mutation related atypical haemolytic uremic syndrome (aHUS)	Davin JC;Groothoff JW;Bemelman FJ;Bouts AH;	2011	3	NR	NR	18 y follow-up of 3 sisters (including monozygotic twins) with aHUS and the same CFH mutation	Older sister: after 14 y dialysis
Interim analysis of phase II efficacy and safety data for eculizumab in patients with atypical haemolytic uremic syndrome (aHUS) receiving chronic plasma exchange/infusion	Goodship THJ;Muus P;Legendre C;Douglas K;Hourmant M;Delmas Y;Herthelius M;Trivelli A;Loirat C;Bedrosian C;Licht C;	2011	20	Median age 28 years	NR	Controlled, open-label, single-arm, 26-week phase II study 20 aHUS patients received eculizumab	10% were on dialysis. Primary endpoint was TMA event-free status no new dialysis

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Eculizumab is an effective long-term treatment in patients with Atypical Haemolytic Uremic Syndrome (aHUS) resistant to plasma exchange/infusion (PE/PI): Results of an extension study	Greenbaum L;Babu S;Furman RR;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Loirat C;Bedrosian CL;Legendre C;	2011	17	Median age 28 years	NR	In a 26-wk phase II trial, pts receiving ECU, Pts ≥12 yrs with aHUS and persistent TMA	5 patients (29%) required dialysis at baseline. With sustained ECU therapy, only 1 of the 5 pts at baseline continued on to require dialysis and no patient newly required dialysis (as of data cut off
Eculizumab in adolescents/adult patients with atypical haemolytic uremic syndrome resistant to plasma exchange/infusion: A phase II efficacy and safety study	Loirat C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Greenbaum L;Bedrosian CL;Zimmerhackl LB;Legendre C;	2011	17	NR	NR	Phase II, controlled, open-label, single-arm 26-week study. Patients > =12 years with PE/PI-resistant aHUS	29% were on dialysis
Eculizumab (ECU) significantly improves Health-Related Quality of Life (HRQoL) in patients with atypical haemolytic uremic syndrome (aHUS)	Muus P;Licht C;Goodship THJ;Greenbaum L;Bedrosian CL;Loirat C;Legendre C;	2011	17 aHUS pts	Median age 28 yrs	NR	2 prospective, controlled, single-arm phase II trials of aHUS pts receiving ECU	29% were on dialysis immediately prior to ECU
Atypical haemolytic uremic syndrome (ahus). A single centre experience	Adragna MS;Balestracci AA;Caletti MG;	2010	11 children	Median age onset: 0.66 months	NR	aHUS pts in institution	10 needed acute dialysis

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Renal replacement therapy in children with haemolytic uremic syndrome in belarus: First 5 years experience	Baiko SV;Sukalo AV;Tur NI;	2010	103 (3 aHUS cases)	Mean age of 2,08+/-2,47 years at the time of admission to hospital	NR	children in Belarus from Jan 2005 to Jan 2010	74 children (71.8%) required dialysis (59 PD and 15 HD) (HUS and aHUS pts)
5 year review of haemolytic uraemic syndrome in Ireland	Bruton K;O'Grady M;Burns K;Cunney R;Waldron M;Riordan M;Awan A;	2010	63 (5 aHUS children)	NR	Ireland	children (<16 years) presenting with HUS between January 2005 and December 2009 to two tertiary paediatric nephrology centres serving the entire population of Ireland	32 children were dialysed - peritoneal dialysis was used in 26. (all pts)
Early intensive plasma exchange (PEX) for atypical haemolytic uraemic syndrome (AHUS) may slow progression to end-stage renal failure (ESRF)	Kim J;Goodship T;Tizard J;Inward C;	2010	3 children	Mean age 10,6 months	NR	3 patients with diarrhoea negative aHUS presented with acute renal failure and severe hypertension	Patients 1-3 respectively: Daily PEX was commenced early following presentation in addition to dialysis. This resulted in HUS remission and cessation of dialysis after 2 weeks, 9 days and 2 weeks
Factor H antibody of Japanese children with atypical haemolytic uremic syndrome	Maekawa K;Shibano T;Takagi N;Sawaki J;Mae H;Hattori M;Tanizawa T;Kawashima F;Nishimura M;	2010	13 children	Mean age of 5.3	NR	CFH and anti CFH antibody in 13 children with atypical HUS from 2005 to 2008	positive group (2 boys and 1 girl) received plasma pheresis or hemodialysis or peritoneal dialysis

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Haemolytic uremic syndrome (HUS) in children - Follow-up and prognosis	Moczulska A;Zachwieja K;Slowiaczek E;Drozdz D;Ogarek I;Wilkosz K;Stec Z;Kwinta-Rybicka J;Miklaszewska M;Pietrzyk JA;	2010	23 (in 9 atypical D-HUS) Children	NR	NR	children with HUS treated 1996-2009	4 dialysis
Atypical haemolytic-uremic syndrome:an etiological and clinical analysis of 26 cases	Yu Y;Pei F;Zhao B;Hu Z;	2010	18	NR	NR	patients with atypical haemolytic-uremic syndrome (aHUS) aHUS in our hospital from January 2003 to December 2009	6 with PE and HD, and 1 with PE plus CVVH and HD 4 patients were treated with HD alone, and 1 patient was treated with HD and CVVH
The Haemolytic-Uremic Syndrome	Ramos S;Gomes L;Sarmento A;Faria MS;Costa T;Mota C;Pereira E;	2001	25 Children	NR	Portugal	children with HUS admitted in Nephrology Department of Hospital Maria Pia. from January 1989 to December 2000	22% of cases presented with oligoanuric acute renal failure but all of them required dialysis
Haemolytic uraemic syndrome. Clinical features, treatment and prognostic indicators	Wende-Fischer R;Hoyer PF;Offner G;Brodehl J;	1996	61 children (an atypical type in 13 patients)	Median age 3.1 years	NR	61 children with haemolytic uraemic syndrome we analysed clinical and laboratory factors and different therapies	dialysis treatment was performed in 49 patients (all pts HUS and aHUS)

Table E7: Summary of studies reporting resource use information: transplant resources

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Transplant resources used							
Atypical hemolytic uremic syndrome in the Tunisian population	Leban N;Aloui S;Touati D;Lakhdhar R;Skhiri H;Lefranc G;Achour A;Elmay M;Lopez-Trascasa M;Sanchez-Corral P;Chibani J;Haj KA;	2011	4 adults	Mean age 36 years	Tunisia	Four cases of atypical HUS in adults admitted in the Nephrology Department of Fattouma Bourguiba Universitary Hospital in Monastir between 2000 and 2008	Patient 2: received a cadaveric kidney transplantation after three years of chronic hemodialysis treatment, and no recurrence of aHUS on the renal allograft was seen thereafter
Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype	Marina Noris, Jessica Caprioli, Elena Bresin, Chiara Mossali, Gaia Pianetti, Sara Gamba, Erica Daina, Chiara Fenili, Federica Castelletti, Annalisa Sorosina,Rossella Piras, Roberta Donadelli, Ramona Maranta,Irene van der Meer, Edward M. Conway,Peter F. Zipfel, Timothy H. Goodship, and Giuseppe Remuzzi	2010	273	NR	58% from Italy, 15% from other European countries, 14% from North America, 2% from South America, 2% from Africa, 1% from Asia, and 8% from the Middle East.	Patients registered from 1996 to 2007 within the International Registry of Recurrent and Familial HUS/TTP	11 had de novo post-transplant aHUS. Simultaneous kidney and liver transplant was performed in four children with CFH mutations and in a child with combined CFH/CFI mutations. One patient with THBD mutation and one with CFH autoantibodies lost the kidney graft for recurrence. Kidney transplant was performed in three patients with MCP mutations.

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation	Davin JC;Strain L;Goodship TH;	2008	3 children	3.8 years mean age	NR	Three sisters, two of whom are monozygotic twins, with atypical HUS associated with a FH mutation	The older sister was transplanted for the second time at the age of 12 years with a cadaver kidney. Her first renal transplant at the age of 5 years was lost to recurrent HUS within weeks of surgery. Twin 1 was the second to be transplanted
Epidemiology, clinical presentation, and pathophysiology of atypical and recurrent hemolytic uremic syndrome	Zimmerhackl LB;Besbas N;Jungraithmayr T;van de Kar N;Karch H;Karpman D;Landau D;Loirat C;Proesmans W;Prufer F;Rizzoni G;Taylor MC;	2006	167	NR	UK, Netherlands, Sweden, cZechia, Austria, Hungary, Switzerland, Israel, Italy, Turkey, France	onset of the disease 1974-2005 in registry	33 pts. renal transplantation, in 18% of these pts. transplant was successful
Recurrence of hemolytic uremic syndrome after renal transplantation in children: a report of the North American Pediatric Renal Transplant Cooperative Study	Quan A;Sullivan EK;Alexander SR;	2001	4 pts with aHUS	NR	United States, Canada, Mexico, and Costa Rica	Patients within the NAPRTCS registry who developed end-stage renal disease as a result of HUS and have subsequently undergone renal transplantation	The original cohort consisted of 114 HUS patients from 54 participating NAPRTCS centers who had 124 renal transplants. We received survey responses from 33 participating centers describing 61 patients who had 68 renal transplants. The information on those 61 patients (68 transplants) is the basis for the present report

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Recurrence of haemolytic-uraemic syndrome in renal transplants: a single-centre report	Miller RB;Burke BA;Schmidt WJ;Gillingham KJ;Matas AJ;Mauer M;Kashtan CE;	1997	18 aHUS	Not clear	USA (Minnesota)	24 patients, between 31 May 1972 and 31 December 1994, with a primary diagnosis of HUS underwent renal trans plantation at the University of Minnesota.	36 transplants (21 primary transplants, 6 second transplants, and 9 third, fourth or fifth grafts)
Heterogeneity of atypical haemolytic uraemic syndromes	Neuhaus TJ;Calonder S;Leumann EP;	1997	23 children	Median age 4.9 years	Switzerland	Clinical and laboratory features of 23 children with D−HUS	5 children underwent cadaveric renal transplantation
Haemolytic uraemic syndrome: prognostic factors in children over 3 years of age	Renaud C;Niaudet P;Gagnadoux MF;Broyer M;Habib R;	1995	21 with aHUS children	Mean age 30.2 months	France	42 children over 3 years old who presented HUS at Necker-Enfants Malades Hospital (Paris, France) between 1955 and 1990	Six patients were transplanted
Eculizumab in adolescents/adult patients with atypical hemolytic uremic syndrome resistant to plasma exchange/infusion: A phase II efficacy and safety study	Loirat C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Greenbaum L;Bedrosian CL;Zimmerhackl LB;Legendre C;	2011	17	NR	NR	Phase II, controlled, open-label, single-arm 26-week study. Patients > =12 years with PE/PI-resistant aHUS	41% had a kidney transplant
Renal transplantation in atypical hemolytic uremic syndrome (AHUS) update of the international HUS registry (HUSNET)	Riedl M;Hofer J;Rosales A;Wurzner R;Giner T;Zimmerhackl LB;Jungraithmayr TC;	2011	26	NR	NR	Since 2001 the HUS study group (www.hus-online.at) is collecting data and performs complement analysis in patients with atypical HUS	49 renal transplantations were performed

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Atypical hemolytic uremic syndrome (aHUS). A single center experience	Adragna MS;Balestracci AA;Caletti MG;	2010	11 children	Median age onset: 0.66 months	NR	aHUS pts. in institution	5 patients underwent cadaveric kidney transplants
Transplantation in atypical hemolytic uremic syndrome	Riedl M;Hofer J;Rosales A;Yeutukhova Y;Jungraithmayr TC;Zimmerhackl LB;	2010	25	NR	NR	Patients with atypical STEC negative HUS.	47 renal transplantations

Table E8: Summary of studies reporting resource use information: hospitalisation

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Hospitalization resources used							
Hemolytic-Uremic Syndrome in Uberlandia, MG, Brazil	Bonetti V;Mangia CM;Zuza JM;Barcelos MO;Fonseca MM;Nery SP;Carvalhaes JT;Andrade MC;	2011	27 children	Median age 14 months	Brazil	Children diagnosed with HUS from January 1, 1994 to January 31, 2004 in the pediatric nephrology department of the Hospital de Clinicas, Universidade Federal de Uberlandia, MG, Brazil,	The mean hospital stay was 24 days (range: 13 to 36 days). [table] / The mean length of hospital stay was 25 days (6 to 70 days)
Hemolytic-uremic syndrome in Switzerland: a nationwide surveillance 1997-2003	Schifferli A;von Vigier RO;Fontana M;Sparta G;Schmid H;Bianchetti MG;Rudin C;	2010	6 children (with aHUS)	Median age 21 months (for all the group not exclusively aHUS pts)	Switzerland	National study through the Swiss Pediatric Surveillance Unit 114 HUS cases	Hospital stay Duration, days 16 (1–60)

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Long-term outcome of children previously on dialysis therapy for hemolytic uremic syndrome	Szczepa+õska M;Szprynger K;Niwi+õska-Faryna B;Muszewska E;	2008	19 aHUS children	Mean age of 46.3 ± 50.0 months for all the group of pts	Poland	HUS hospitalized pts at the Department and Clinics of Pediatrics in Zabrze of Silesian Medical University in Katowice from 1990 to 2006.	The mean hospitalization time was 49.1 ± 34.9 days. (range: 9–152 days).
Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features	Elliott EJ;Robins-Browne RM;O'Loughlin EV;Bennett-Wood V;Bourke J;Henning P;Hogg GG;Knight J;Powell H;Redmond D;	2001	14 aHUS children	median age of cases at diagnosis was 31 months	Australia	Children under 15 years presenting with microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal impairment were identified through the Australian Paediatric Surveillance Unit with monthly case notification from paediatricians, July 1994 to June 1998.	Ninety one (92%) children were hospitalised for a median (interquartile range) of 14 (7–21) days (all cases, not exclusively aHUS)

Table E9: Summary of studies reporting resource use information: plasma exchange resources

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Plasma exchange resources used							
Prognostic value of renal pathological findings in children with atypical hemolytic uremic syndrome	Mehrazma M;Hooman N;Otukesh H;	2011	29 children	NR	Iran	AHUS patients between 1992 and 2005 in Ali Asghar Children Hospital.	13 pts had received fresh frozen plasma, and 11 had received fresh frozen plasma with intravenous immunoglobulin

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Plasma therapy for atypical haemolytic uraemic syndrome associated with heterozygous factor H mutations	Kim JJ;Goodship TH;Tizard J;Inward C;	2011	3 children	Mean age 10.6 months	UK	Patients with heterozygous CFH mutations associated with aHUS	Plasma Therapy was started within 3 days of presentation for all three pts. The PEX regimen consisted of 70 ml/kg volume exchange with fresh frozen plasma (FFP) each session. When FFP infusions were given alone, the dose was 15–20 ml/kg rounded to the nearest pooled unit. The FFP brand was Octaplas
Atypical hemolytic uremic syndrome in the Tunisian population	Leban N;Aloui S;Touati D;Lakhdhar R;Skhiri H;Lefranc G;Achour A;Elmay M;Lopez-Trascasa M;Sanchez-Corral P;Chibani J;Haj KA;	2011	4 adults	Mean age 36 years	Tunisia	Four cases of atypical HUS in adults admitted in the Nephrology Department of Fattouma Bourguiba Universitary Hospital in Monastir between 2000 and 2008	Patient 1: Plasma exchange (60 mL/Kg of fresh frozen plasma per session) was carried out, with no improvement. Patient 2: The patient was treated with ten sessions of plasma exchange (40 ml/Kg of fresh-frozen plasma per session), with no improvement, patient 3: There was no improvement after eight sessions of plasma exchange (40 ml/Kg of fresh-frozen plasma per session)
Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations	Fakhouri F;Roumenina L;Provot F;Sallee M;Caillard S;Couzi L;Essig M;Ribes D;Dragon-Durey MA;Bridoux F;Rondeau E;Fremeaux-Bacchi V;	2010	21 adults	Mean age 28 years	France	French cohort of adult patients with TMA	Treatment consisted mainly of plasma exchange (15 of 18, 83%)

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Pulse cyclophosphamide therapy and clinical remission in atypical hemolytic uremic syndrome with anti-complement factor H autoantibodies	Boyer O;Balzamo E;Charbit M;Biebuyck-Gouge N;Salomon R;Dragon-Durey MA;Fremeaux-Bacchi V;Niaudet P;	2010	3 children	Mean age 5.8 years	NR	3 children with atypical hemolytic uremic syndrome associated with anti–complement factor H (CFH) autoantibodies	Patient 1: The patient received daily fresh frozen plasma (FFP) infusions from day (D)1-D7, then tapered to every other day. And thereafter he was treated with 12 PEs with fresh frozen plasma replacement from D21-D35, Patient 2: received 3 fresh frozen plasma infusions (10 mL/d/kg body weight) without remission, patient 3: he was treated with 2 PEs (D11 and D14)
Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype	Marina Noris, Jessica Caprioli, Elena Bresin, Chiara Mossali, Gaia Pianetti, Sara Gamba,Erica Daina, Chiara Fenili, Federica Castelletti, Annalisa Sorosina, Rossella Piras, Roberta Donadelli,Ramona Maranta Irene van der Meer,Edward M. Conway,Peter F. Zipfel,Timothy H. Goodship, and Giuseppe Remuzzi	2010	273	NR	58% from Italy, 15% from other European countries, 14% from North America, 2% from South America, 2% from Africa, 1% from Asia, and 8% from the Middle East.	Patients registered from 1996 to 2007 within the International Registry of Recurrent and Familial HUS/TTP	131 children and 51 adults responded to plasma exchange. Overall, 70% of episodes (50% of patients) responded to plasma without differences between sporadic and familial cases. A better response to plasma treatment was observed in children than in adults

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Atypical Hemolytic Uremic Syndrome Associated With Complement Factor H Autoantibodies and CFHR1/CFHR3 Deficiency	Lee BH;Kwak SH;Il Shin J;Lee SH;Choi HJ;Kang HG;Ha IS;Lee JS;Dragon-Durey MA;Choi Y;Il Cheong H;	2009	3 children	Mean age 8.6 years at onset	NR	Three patients clinically diagnosed as aHUS	Patient 1: 10 sessions of daily plasmapheresis followed by a week of intermittent plasmapheresis (three times per week), patients 2 undergone PE and PI and patient 3 undergone PI

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation	Davin JC;Strain L;Goodship TH;	2008	3 children	3.8 years mean age	NR	three sisters, two of whom are monozygotic twins, with atypical HUS associated with a FH mutation	1 twin: Plasma exchange (PE) was initiated, and ten daily sessions of PE (40 ml/kg per session) undertaken. She received thereafter three sessions of five plasma infusions (10 ml/kg) in response to recurrent thrombocytopaenia and haemolysis with good effect. 2nd twin: Daily PE was performed until normalisation of plasma creatinine after 3 weeks (132 µmol/l to 61 µmol/l) Thereafter, PE was undertaken once every 2 weeks. Three and 19 months later, thrombocytopaenia and haemolysis in association with a respiratory tract infection prompted a temporary increase in the frequency of PE to daily. Following the second relapse, weekly PE was undertaken for 6 months, followed by a frequency of once every 2 weeks indefinitely. Older sister: PE was undertaken immediately prior to transplantation, daily for the first postoperative week, and then progressively tapered to once every 2 weeks by 2 months post-transplant

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Hemolytic uremic syndrome in Kuwaiti Arab children	Al-Eisa A;Al-Hajeri M;	2001	11 aHUS children	Mean age at presentation was 34.2±38.2 months in the D– HUS group	Kuwait	Twenty-five children with HUS diagnosed between January 1985 and January 2000 in the Pediatric Nephrology Unit at Mubarak Al-Kabeer Hospital	Therapeutic modalities used, in addition to dialysis, included fresh frozen plasma infusions in 19 patients (76%) of both D+ and D– HUS groups
Recurrence of hemolytic uremic syndrome after renal transplantation in children: a report of the North American Pediatric Renal Transplant Cooperative Study	Quan A;Sullivan EK;Alexander SR;	2001	4 aHUS	NR	United States, Canada, Mexico, and Costa	Patients within the NAPRTCS registry who developed end-stage renal disease as a result of HUS and have undergone renal transplantation	Treatment of HUS recurrence in these six renal transplants included no treatment in one, infusion of fresh-frozen plasma in four, plasmapheresis in two, and administration of defibrotide in two.. One patient was treated with both fresh-frozen plasma infusion and plasmapheresis. The patient who had two renal allografts was treated with plasma infusion and defibrotide each time
Heterogeneity of atypical haemolytic uraemic syndromes	Neuhaus TJ;Calonder S;Leumann EP;	1997	23 children	Median age 4.9 years	Switzerland	Clinical and laboratory features of 23 children with D−HUS,	7 patients, all requiring dialysis, underwent plasma exchange

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Haemolytic uraemic syndrome: prognostic factors in children over 3 years of age	Renaud C;Niaudet P;Gagnadoux MF;Broyer M;Habib R;	1995	21 with aHUS children	Mean age 30.2 months	France	42 children over 3 years of age who presented with HUS at Necker-Enfants Malades Hospital (Paris, France) between 1955 and 1990	Three patients received 10-20 fresh-frozen plasma infusions, associated with plasma exchange during the 1st month of the disease, and 1 received only plasma exchange. The 4 patients recovered normal renal function. The remaining patient received successively 7 plasma exchanges, 6 infusions of fresh-frozen plasma, 2 plasma exchanges and 5 infusions of fresh-frozen plasma because of relapses of both the renal and haematological manifestations
Eculizumab is effective in patients resistant to plasma exchange/infusion with atypical haemolytic uremic syndrome (AHUS)	Bedrosian C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Loirat C;Greenbaum L;Zimmerhaekl L;Legendre C;	2011	17 aHUS pts.	15 of 17 pts group with median age 28 years	NR	26-week, controlled, open-label, single-arm trial, pts > 12 years were enroled with plasma-resistant aHUS	Pts received eculizumab 900 mg/week (4 weeks), 1200 mg (week 5), and then 1200 mg q2 weeks (plus a meningococcal vaccine). Primary end-point: change in platelet (plt) count (a measure of TMA) over 26 weeks. Secondary endpoints: TMA event-free status (≥12 weeks of stable plt count, no plasma exchange/infusion and no new dialysis), TMA intervention rate (no. of plasma and new dialysis events/ pt/day), renal function, PK/PD and safety. Plt count increased from baseline to week 26 by a point estimate 73 x 109/L (95% CI: 40-105 x 109/L) (primary endpoint; P = 0.0001).

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Prophylactic plasmapheresis (PE) and eculizumab (EC) allow long term renal function preservation in FH mutation related atypical haemolytic uremic syndrome (aHUS)	Davin JC;Groothoff JW;Bemelman FJ;Bouts AH;	2011	3	NR	NR	18 y follow-up of 3 sisters (including monozygotic twins) with aHUS and the same CFH mutation	Intensive PE was used at first episode or recurrence: daily sessions until pl.creat normalisation followed by progressive tapering and indefinitely prolongation. in case of Tx: pre-Tx session followed by daily PE for one week, tapered until 1PE/w and indefinitely prolonged. At month 12 post-Tx3, PE was shift to EC because of severe reactions to plasma. Twin 1: after 2 years dialysis, successful first Tx (Tx1) despite several CMV infection-associated recurrences. Pl. creat: 150 mumol/L at age 17 y, 8 y after Tx1. c/ twin 2: complete recovery after first episode. Pl.creat. 58 mumol/L at age 17 y, 10 y after first HUS episode
Interim analysis of phase II efficacy and safety data for eculizumab in patients with atypical haemolytic uremic syndrome (aHUS) receiving chronic plasma exchange/infusion	Goodship THJ;Muus P;Legendre C;Douglas K;Hourmant M;Delmas Y;Herthelius M;Trivelli A;Loirat C;Bedrosian C;Licht C;	2011	20	median age 28 years	NR	Controlled, open-label, single-arm, 26-week phase II study 20 aHUS patients received eculizumab	aHUS patients on 12 years plasma exchange/infusion completed an 8-week observation period before initiating eculizumab (900 mg/week for 4 weeks, 1200 mg at week 5, then 1200 mg q2 weeks). Patients received a meningococcal vaccine = 2 weeks before eculizumab.); 45% received 2-3 plasma exchange/infusion sessions/week;

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Eculizumab in adolescents/adult patients with atypical haemolytic uremic syndrome resistant to plasma exchange/infusion: A phase II efficacy and safety study	Loirat C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Greenbaum L;Bedrosian CL;Zimmerhackl LB;Legendre C;	2011	17	NR	NR	Phase II, controlled, open-label, single-arm 26-week study. Patients > =12 years with PE/PI-resistant aHUS	Patients > =12 years with PE/PI-resistant aHUS (persistent TMA despite > =4 PE/PI sessions
Eculizumab (ECU) significantly improves Health-Related Quality of Life (HRQoL) in patients with atypical haemolytic uremic syndrome (aHUS)	Muus P;Licht C;Goodship THJ;Greenbaum L;Bedrosian CL;Loirat C;Legendre C;	2011	17 aHUS pts	Median age 28 yrs	NR	2 prospective, controlled, single-arm phase II trials of aHUS pts receiving ECU,	In trial C08-003, 20 pts previously received chronic PE/PI (> =1 every 2 wks and <3 per wk for > =8 wks prior to ECU
Anti-factor H antibodies in Japanese children with atypical haemolytic uremic syndrome	Nishimura M;Maekawa K;Kawashima F;Takagi N;Sawaki J;Takahashi C;Mae H;Hattori M;Tanizawa T;	2011	14 Children	NR	NR	Cases of aHUS associated with anti-CFH-ab, and show clinical features in 14 cases of Japanese aHUS children	All 4 patients of positive anti-CFH-ab needed intensive immunosuppressive therapy after plasmapheresis.
Atypical haemolytic uremic syndrome (ahus). A single centre experience	Adragna MS;Balestracci AA;Caletti MG;	2010	11 children	Median age onset: 0.66 months	NR	aHUS pts in institution	7pts: plasma infusions.

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
5 year review of haemolytic uraemic syndrome in Ireland	Bruton K;O'Grady M;Burns K;Cunney R;Waldron M;Riordan M;Awan A;	2010	63(5 aHUS children)		Ireland	children (<16 years) presenting with HUS between January 2005 and December 2009 to two tertiary paediatric nephrology centres serving the entire population of Ireland	11 underwent plasma exchange (4 atypical cases)
Early intensive plasma exchange (PEX) for atypical haemolytic uraemic syndrome (AHUS) may slow progression to end-stage renal failure (ESRF)	Kim J;Goodship T;Tizard J;Inward C;	2010	3 children	mean age 10,6 months	NR	3 patients with diarrhoea negative aHUS presented with acute renal failure and severe hypertension	Patients 1-3 respectively). Daily PEX was commenced. Patient 2 had slow tapering of PEX over 4 months to fortnightly sessions and relapsed when PEX was extended to four weekly
Plasmatherapy in atypical haemolytic uremic syndrome, French cohort	Kwon T;Biebuyck N;Cailliez M;Broux F;Macher MA;Niaudet P;Tsimaratos M;Deschenes G;Fremeaux V;Loirat C;	2010	10 children	mean age 6 months	NR	10 children treated by long term PT	All patients received PT (fresh frozen plasma infusions in 6, plasma exchanges in 4)
Factor H antibody of Japanese children with atypical haemolytic uremic syndrome	Maekawa K;Shibano T;Takagi N;Sawaki J;Mae H;Hattori M;Tanizawa T;Kawashima F;Nishimura M;	2010	13 children	mean age of 5.3	NR	CFH and anti CFH antibody in 13 children with atypical HUS from 2005 to 2008	positive group (2 boys and 1 girl) was performed plasma pheresis or hemodialysis or peritoneal dialysis)

Title	Author(s)	Publication date	N (children-adult)	Age (median –mean)	Country	Study population	Resources
Haemolytic uremic syndrome (HUS) in children - Follow-up and prognosis	Moczulska A;Zachwieja K;Slowiaczek E;Drozdz D;Ogarek I;Wilkosz K;Stec Z;Kwinta-Rybicka J;Miklaszewska M;Pietrzyk JA;	2010	23 (in 9 atypical D-HUS) Children	NR	NR	children with HUS treated 1996-2009	Plasmapheresis was performed in 6/9 D- pts . 2 received fresh frozen plasma
Atypical haemolytic-uremic syndrome:an etiological and clinical analysis of 26 cases	Yu Y;Pei F;Zhao B;Hu Z;	2010	18	NR	NR	patients with atypical haemolytic-uremic syndrome (aHUS) aHUS in our hospital from January 2003 to December 2009	15 patients were treated with plasma exchange (PE), among them .8 patients received plasma infusion.

Table E10: Summary of studies reporting natural history of aHUS

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Prognostic value of renal pathological findings in children with atypical hemolytic uremic syndrome	Mehrazma M;Hooman N;Otukesh H;	2011	29 children	NR	Iran	AHUS pts between 1992 and 2005 in Ali Asghar Children Hospital.	The last follow-up visits were conducted an average of 3.7 years after disease onset (range, 0.03 to 12.5 years). Seven patients (24.1%), who were on hemodialysis or continuous ambulatory peritoneal dialysis, died of malignant hypertension, pulmonary edaema, and congestive heart failure. One of the 3 deaths occurred in the first 3 months of diagnosis. All deaths occurred in those who received fresh frozen plasma. Twenty-two children (75.9%) were still alive, 3 of who returned to their hometowns. Those who were hypertensive at the time of admission developed CKD on follow-up (RR, 3.7; 95% CI, 1.6 to 8.7; p < .001). Mortality did not correlate with gender (P = .60), hypertension (P = .09), administration of fresh frozen plasma (P = .70), or administration of anti-hypertensives (P = .51). In all, 7 patients (24.1%) had normal kidney function and blood pressure, 18 (62.1%) had proteinuria (3 with hypertension and 3 with isolated proteinuria), 1 (3.4%) had persistent hematuria, and 12 (41.4%) suffered from CKD concomitant with hypertension and proteinuria. The most glomerular involvements were reduction in the capillary lumen, thickening of the capillary wall, mesangial cell proliferation, and fibrillary changes

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Plasma therapy for atypical haemolytic uraemic syndrome associated with heterozygous factor H mutations	Kim JJ;Goodship TH;Tizard J;Inward C;	2011	3 children	Mean age 10.6 months	UK	Patients with heterozygous CFH mutations associated with aHUS	Patient 1 initially had only 3 days of plasma filtration (with FFP replacement) because of associated hypotension. Patient 2 had a good response to daily PEX, which was continued for 2 weeks and then gradually reduced in frequency to once every 2 weeks. Patient 3 initially had daily PEX for 2 weeks and this was decreased in frequency to twice a week. Patient 1 recovered 50% of renal function after first presentation. She had four relapses and started peritoneal dialysis 41 months after presentation. Mutation screening of CFH showed a missense mutation (c.3546 G > T, p.Arg1182Ser) in exon 23. PEX in patient 2 was slowly tapered over 4 months to fortnightly sessions, but she relapsed when PEX was extended to every 4 weeks. Renal function remained normal 12 months post-presentation. Mutation screening of CFH showed a mutation in exon 23 (c.3590 T > C, p.Val1197Ala) and two additional sequence variants in exons 3 and 4. Patient 3 had two relapses associated with intercurrent illnesses concurrent with reducing PEX to weekly doses. Renal function was normal 5 months post-presentation. All three patients showed a good response to PEX with improved renal function both initially and following a relapse.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Hemolytic-Uremic Syndrome in Uberlandia, MG, Brazil	Bonetti V;Mangia CM;Zuza JM;Barcelos MO;Fonseca MM;Nery SP;Carvalhaes JT;Andrade MC;	2011	27 children	Median age 14 months	Brazil	Children diagnosed with HUS during a from January 1, 1994 to January 31, 2004 in the pediatric nephrology department of the Hospital de Clinicas, Universidade Federal de Uberlandia, MG, Brazil,	The most frequent symptoms were fever and vomiting, which were observed in 23 patients (85.1%). Nine patients (33.3%) had seizures, three (11.1%) had cardiac involvement, and two patients (7,4%) developed acute pulmonary edaema. With regard to the outcome, 2 patients (7.4%) died, 3 patients (11%) developed chronic kidney disease, and 21 (77.8%) developed hypertension
Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations	Fakhouri F;Roumenina L;Provot F;Sallee M;Caillard S;Couzi L;Essig M;Ribes D;Dragon-Durey MA;Bridoux F;Rondeau E;Fremeaux-Bacchi V;	2010	21 adults	Mean age 28 years	France	French cohort of adult patients with TMA	Long-term outcome was poor: 76% (16 of 21) of patients had reached ESRF or had undergone renal transplantation at last follow-up. Sixteen pregnancies led to a live birth, and one pregnancy was complicated by an early fetal loss
Pulse cyclophosphamide therapy and clinical remission in atypical hemolytic uremic syndrome with anti-complement factor H autoantibodies	Boyer O;Balzamo E;Charbit M;Biebuyck-Gouge N;Salomon R;Dragon-Durey MA;Fremeaux-Bacchi V;Niaudet P;	2010	3 children	Mean age 5.8 years	NR	3 children with atypical hemolytic uremic syndrome associated with anti–complement factor H (CFH) autoantibodies	All 3 patients show a homozygous deletion mutation of the CFHR1 and CFHR3 genes. Cyclophosphamide pulses with PE may lead to a prolonged decrease in CFH antibody titers and a favorable outcome of atypical hemolytic uremic syndrome and kidney function

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Hemolytic-uremic syndrome in Switzerland: a nationwide surveillance 1997-2003	Schifferli A;von Vigier RO;Fontana M;Sparta G;Schmid H;Bianchetti MG;Rudin C;	2010	6 children (with aHUS)	Median age 21 months (for all the group not the aHUS pts)	Switzerland	National study through the Swiss Pediatric Surveillance Unit 114 HUS cases	The average annual incidence was 1.42 cases (range, 0.61–1.92) per 100,000 children ≤16 years of age. None of the patient with atypical HUS (D−) died.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation	Davin JC;Strain L;Goodship TH;	2008	3 children	3.8 years mean age	NR	three sisters, two of whom are monozygotic twins, with atypical HUS associated with a FH mutation	This response to intensive PE prompted to undertake transplantation with prophylactic plasma therapy in the two sisters (older and 1st twin). The older sister was transplanted for the second time at the age of 12 years with a cadaver kidney. Her first renal transplant at the age of 5 years was lost to recurrent HUS within weeks of surgery. The graft functioned well (plasma creatinine 80 µmol/l) until 2 months post-transplant, when plasma creatinine increased to 200 µmol/l, without either evidence of thromboctyopaenia or significant haemolysis. A clinical diagnosis of acute rejection was made, and treatment commenced with pulse methylprednisolone. A renal biopsy performed 5 days later following a further deterioration in transplant function showed HUS, and despite an increase in the frequency of PE, the graft did not recover. Twin 1 was the second to be transplanted. Ten months post-transplant, she presented with biopsy-proven recurrent HUS associated with primary cytomegalovirus (CMV) infection. The plasma creatinine was 167 µmol/l. After 4 weeks treatment with daily PE and ganciclovir, plasma creatinine stabilised at 90 µmol/l. When ganciclovir was stopped 6 months later, there was a further episode of recurrent HUS, and plasma creatinine increased to 187 µmol/l. Again, intensification of PE and the use of ganciclovir resulted in recovery of graft function. Continuous CMV prophylaxis with acyclovir was instituted, and no further episodes of either CMV reactivation or recurrent HUS were seen. Five years after transplantation, plasma creatinine was 127 µmol/l, and transplant biopsy showed allograft nephropathy but no HUS activity.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Long-term outcome of children previously on dialysis therapy for hemolytic uremic syndrome	Szczepa+õska M;Szprynger K;Niwi+õska-Faryna B;Muszewska E;	2008	19 aHUS children	Mean age of 46.3 ± 50.0 months for all the group of pts	Poland	HUS hospitalized pts at the Department and Clinics of Pediatrics in Zabrze of Silesian Medical University in Katowice from 1990 to 2006.	End−stage renal failure was established in 3 children (8.4%). Chronic renal disease of grades 2−4 was found in 6 (16.7%) children, arterial hypertension in 22 (61%) which required medication with mean 2.4 ± 1.3 hypotensive agents, and proteinuria was present in 6 (16.7%) children. In 5 children (13.9%) organ complications of hypertension, such as left ventricle thickening, were detected. Negative correlation between the duration of renal replacement and mean glomerular filtration rate (GFR) after 5 years of observation was observed.
Epidemiology, clinical presentation, and pathophysiology of atypical and recurrent hemolytic uremic syndrome	Zimmerhackl LB;Besbas N;Jungraithmayr T;van de Kar N;Karch H;Karpman D;Landau D;Loirat C;Proesmans W;Prufer F;Rizzoni G;Taylor MC;	2006	167	NR	UK, Netherlands, Sweden, Czechia, Austria, Hungary, Switzerland, Israel, Italy, Turkey, France	onset of the disease 1974-2005 in registry	prevalence of aHUS 3.3 per million in child population
Hemolytic uremic syndrome in Kuwaiti Arab children	Al-Eisa A;Al-Hajeri M;	2001	11 aHUS children	Mean age at presentation was 34.2±38.2 months in the D– HUS group	Kuwait	Twenty-five children with HUS diagnosed between January 1985 and January 2000 in the Pediatric Nephrology Unit at Mubarak Al-Kabeer Hospital	Mortality was significantly higher in the D– HUS patients (P<0.0001). Recurrence of HUS was documented in 63.3% of the D– HUS group

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Recurrence of hemolytic uremic syndrome after renal transplantation in children: a report of the North American Pediatric Renal Transplant Cooperative Study	Quan A;Sullivan EK;Alexander SR;	2001	4 aHUS	NR	United States, Canada, Mexico, and Costa	Patients within the NAPRTCS registry who developed end-stage renal disease as a result of HUS and have subsequently undergone renal transplantation.	For living donors, graft survival rates between HUS and non-HUS patients were equivalent (Fig. 1A). In cadaveric donor grafts, HUS patients tended to have a lower graft survival compared with their non-HUS counterparts, although the difference was not statistically significant (Fig. 1B). Most graft losses in the HUS patients occurred during the first 6 months after transplantation. Excluding HUS recurrence, the majority of grafts in both the HUS and non-HUS patients were lost because of technical difficulties (19%), acute rejection (22%), and chronic rejection (28%). We found that four of five patients with recurrence of HUS in the allograft initially presented with atypical HUS,
Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features	Elliott EJ;Robins-Browne RM;O'Loughlin EV;Bennett-Wood V;Bourke J;Henning P;Hogg GG;Knight J;Powell H;Redmond D;	2001	14 aHUS children	Median age of cases at diagnosis was 31 months	Australia	Children under 15 years presenting with microangiopathic haemolytic anaemia, thrombocytopaenia, and acute renal impairment were identified through the Australian Paediatric Surveillance Unit with monthly case notification from pediatricians, July 1994 to June 1998.	The reported annual incidence of HUS (with 95% CI) was 0.64 (0.52 to 0.78) per 105 children under 15 years. Incidence was significantly higher in children under 5 years (1.35 (1.06 to 1.72) per 105) than in those aged 5–14 years (0.28 (0.18 to 0.39) per 105; Fisher's exact test, $p < 0.0001$). When outbreak cases were excluded from the analysis, the overall incidence was slightly, though not significantly lower.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Recurrence of haemolytic-uraemic syndrome in renal transplants: a single-centre report	Miller RB;Burke BA;Schmidt WJ;Gillingham KJ;Matas AJ;Mauer M;Kashtan CE;	1997	18 aHUS	Not clear	USA (Minesota)	Between 31 May 1972 and 31 December 1994, 24 patients with a primary diagnosis of HUS underwent renal trans plantation at the University of Minnesota.	There were 16 episodes of recurrence of HUS involving 14 allografts in 11 patients. Nine of these 11 patients had atypical HUS, one had classical HUS, and one could not be classified. Recurrence began 1 day to 9.4 years after transplantation; 11 of 14 initial recurrences developed within 2 months post-transplant
Heterogeneity of atypical haemolytic uraemic syndromes	Neuhaus TJ;Calonder S;Leumann EP;	1997	23 children	Median age 4.9 years	Switzerland	Clinical and laboratory features of 23 children with D−HUS,	Nineteen (91%) of the 21 surviving children were regularly followed up for a median period of 5.5 years (range 0.5–23.4). Only two infant's not requiring dialysis could not be located; at discharge their plasma creatinine had almost returned to normal. Five children (26%) recovered completely, including three infants and one neonate who had not received acute dialysis. Of the eight children who had required acute dialysis, only one showed complete recovery, five had moderate squeal (three were also hypertensive), and two boys died, one during the third episode of HUS and one of end stage renal failure six months after a S pneumonia meningitis
Atypical hemolytic-uremic syndrome: a comparison with postdiarrheal disease	Siegler RL;Pavia AT;Hansen FL;Christofferson RD;Cook JB;	1996	22 aHUS children	Median ages 3.5 years	USA, Utah	Patient residents of Utah or surrounding states and had been cared for at the University of Utah Health Sciences Center, or its close affiliate, Primary Children's Medical Center.	There were no deaths in the subset of patients with atypical disease. two of the four patients with atypical disease who had recurrences also had end-stage renal disease. End-stage renal disease occurred in two (9%) of the patients with atypical disease.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Haemolytic uraemic syndrome: prognostic factors in children over 3 years of age	Renaud C;Niaudet P;Gagnadoux MF;Broyer M;Habib R;	1995	21 aHUS children	Mean age 30.2 months	France	42 consecutive children over 3 years of age who presented with HUS at Necker-Enfants Malades Hospital (Paris, France) between 1955 and 1990	Our study shows that not all children over the age of 3 years, but rather only those with D-HUS, are at high risk of morbidity and renal mortality. patients of the second group who had no prodromal diarrhea, the clinical presentation was characterized by an insidious onset, with normal urine output except in 4 patients who were oliguric.
Outcome and prognostic determinants in the hemolytic uremic syndrome of children	Tonshoff B;Sammet A;Sanden I;Mehls O;Waldherr R;Scharer K;	1994	21 aHUS children	Median 3.1 years	Germany	Children with HUS observed from 1971-1988 treated in University Children's Hospital in Heidelberg	10 pts died with ahus
Eculizumab is effective in patients resistant to plasma exchange/infusion with atypical haemolytic uremic syndrome (AHUS)	Bedrosian C;Babu S;Furman R;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Loirat C;Greenbaum L;Zimmerhaekl L;Legendre C;	2011	17 aHUS pts	15 of 17 pts group with median age 28 years	NR	26-week, controlled, open-label, single-arm trial, pts > 12 years were enroled with plasma-resistant aHUS	Fifteen pts (88% 95% CI 64-100%) became TMA event-free. Median TMA intervention rate decreased from 0.88 to 0 events/pt/day ($p < 0.0001$). eGFR improvement > 15 mL/min/ 1.73 m^2 was found in 9/17 pts (53%). Importantly, four of five pts became dialysis-free. PK-PD blood sampling confirmed that eculizumab provided sustained terminal complement blockade. Eculizumab was effective in pts regardless of CRFM. Eculizumab was well tolerated; most common adverse events: headache, anaemia, diarrhoea (mild-moderate). The endpoints were achieved with high clinical and statistical significance. Eculizumab prevented TMA, restored renal function, removed the need for plasma exchange/infusion, and was well tolerated

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Prophylactic plasmapheresis (PE) and eculizumab (EC) allow long term renal function preservation in FH mutation related atypical haemolytic uremic syndrome (aHUS)	Davin JC;Groothoff JW;Bemelman FJ;Bouts AH;	2011	3 children	NR	NR	18 y follow-up of 3 sisters (including monozygotic twins) with aHUS and the same CFH mutation	a/ older sister: after 14 y dialysis and 2 immediate Tx losses by recurrence, successful third Tx (Tx3) despite recurrence at month 8. Severe cerebral artery stenosis present after 12 y dialysis. At month 12 post-Tx3, PE was shift to EC because of severe reactions to plasma. Pl.creat: 125 mumol/L 3 years post Tx3, at 20 y age; b/ twin 1: after 2 years dialysis, successful first Tx (Tx1) despite several CMV infection-associated recurrences. Pl. creat: 150 mumol/L at age 17 y, 8 y after Tx1. c/ twin 2: complete recovery after first episode. Pl.creat. 58 mumol/L at age 17 y, 10 y after first HUS episode. No cerebral artery stenosis demonstrated in both twins after 10 y evolution. Conclusions: Intensive en prophylactic PE, eventually shifted to EC allows long term preservation of renal function of native kidney and of transplant and might prevent large vessels stenosis in FH mutation-related aHUS
Interim analysis of phase II efficacy and safety data for eculizumab in patients with atypical haemolytic uremic syndrome (aHUS) receiving chronic plasma exchange/infusion	Goodship THJ;Muus P;Legendre C;Douglas K;Hourmant M;Delmas Y;Herthelius M;Trivelli A;Loirat C;Bedrosian C;Licht C;	2011	20	Median age 28 years	NR	Controlled, open-label, single-arm, 26-week phase II study 20 aHUS patients received eculizumab	Most frequent adverse events were diarrhea, headache, hypertension, nausea (mild-moderate). Conclusions: Eculizumab sustained suppression of TMA, leading to permanent discontinuation of chronic plasma exchange/infusion, maintained renal function, and was well tolerated

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Eculizumab is an effective long-term treatment in patients with Atypical Haemolytic Uremic Syndrome (aHUS) resistant to plasma exchange/infusion (PE/PI): Results of an extension study	Greenbaum L;Babu S;Furman RR;Sheerin N;Cohen D;Gaber O;Eitner F;Delmas Y;Loirat C;Bedrosian CL;Legendre C;	2011	17	Median age 28 years	NR	In a 26-wk phase II trial, pts receiving ECU, Pts ≥12 yrs with aHUS and persistent TMA	pts treated with ECU for a mean duration of > 1 yr remain alive, 4 out of 5 pts became dialysis free, and no pt newly required dialysis. This demonstrates that continued ECU treatment significantly transformed the clinical course of aHUS in this pt population. In addition, long-term ECU therapy suppressed TMA and dramatically improved renal function. These long-term follow-up data further strengthen the evidence for ECU as the new standard of care for aHUS
Eculizumab (ECU) therapy for atypical haemolytic uremic syndrome (AHUS) in paediatric patients: Efficacy and safety outcomes from a retrospective study	Gruppo R;Rodig N;Vilalta R;Hernandez J;Camacho J;Lapeyraque AL;Sherwinter J;Fremont O;Baudouin V;Simonetti GD;Langman C;	2011	30	NR	NR	aHUS pts receiving > = 1 Ecu dose outside of clinical trials 2007-2009	Ecu efficacy was similar across age groups. Safety was similar to adult/adolescent pts in clinical trials. These results, consistent with those from adult/adolescent trials, show that Ecu treatment is well tolerated and can control TMA, reduce need for PE/PI and improve kidney function, thus showing the promising potential of Ecu as a new standard of care for aHUS.
Estimated patient number of congenital atypical HUS within a TMA patient registry across japan: A registry of Nara medical university	Hayakawa M;Matsumoto M;Yoshida Y;Isonishi A;Kato S;Fujimura Y;	2011	34	NR	Japan	34 patients were assumed to be congenital aHUS	Of 34 patients, 27 (79.4%) had relatives with HUS or TTP, and 15 (44.1%) had childhood episode of unknown thrombocytopenia. Of note, none of the suspected congenital aHUS patients had a history of severe newborn jaundice that required exchange blood transfusion, which is a hallmark for USS.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Eculizumab (ECU) significantly improves Health-Related Quality of Life (HRQoL) in patients with atypical haemolytic uremic syndrome (aHUS)	Muus P;Licht C;Goodship THJ;Greenbaum L;Bedrosian CL;Loirat C;Legendre C;	2011	17 aHUS pts	Median age 28 yrs	NR	2 prospective, controlled, single-arm phase II trials of aHUS pts receiving ECU,	In both cohorts of distinct trial pts, ECU substantially improved HRQoL through Wk 26, and sustained this thereafter during long-term ECU therapy (table). In trial C08-002, improvements were seen as early as Day 7 (0.12, p=0.0346). Point estimate improvement (95% CI) in HRQoL from baseline to 1 yr was 0.32 (0.27-0.36) for C08-002 and 0.09 (0.05-0.14) for C08-003. On an individual pt basis, 87% and 73% of C08-002 and C08-003 pts, respectively, achieved a clinically meaningful change that represented a clinically important large or moderate improvement in HRQoL measures, respectively
Atypical haemolytic uremic syndrome (ahus). A single centre experience	Adragna MS;Balestracci AA;Caletti MG;	2010	11 children	Median age onset: 0.66 months	NR	aHUS pts in institution	4 p.normal renal function, 7 developed CRF: 2 in predialysis medical treatment and 5: ESRD. aHUS was present in younger children, with more hypertension and higher requirement of dialysis. Outcome was unfavourable, with a high rate of recurrence and ESRD. Our results force us to enhance the efforts to identify the mutations in order to select the best treatment for each type of patient
Renal replacement therapy in children with haemolytic uremic syndrome in belarus: First 5 years experience	Baiko SV;Sukalo AV;Tur NI;	2010	103(3 aHUS cases)	average age of 2,08+/-2,47 years at the time of admission to hospital	NR	(HUS) in children in Belarus from Jan 2005 to Jan 2010	The incidence of HUS in Belarus was 4,24 cases/100 000 in children < 5 y and 1,37 cases/100 000 when all children < 15 y were taken into account. The mean time of ambulatory observation was 3,2+/-2,3 y. End-stage renal failure was established in 1 child (1,54%), chronic renal disease at grades 2-4 was revealed in 2 (3,08%) patients, 77,5% of children had the arterial hypertension by discharge from the hospital, in 3 cases (4,6%) severe proteinuria was present.

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
5 year review of haemolytic uraemic syndrome in Ireland	Bruton K;O'Grady M;Burns K;Cunney R;Waldron M;Riordan M;Awan A;	2010	63(5 ahus children)	NR	Ireland	children (<16 years) presenting with HUS between January 2005 and December 2009 to two tertiary paediatric nephrology centres serving the entire population of Ireland	5 patients had atypical HUS - 3 pneumococcal (1 died, 1 long-term sequelae); and 2 with Factor H mutations (1 has renal impairment).
Clinical features of anti-FH auto antibodies-associated HUS: A typical onset but an atypical outcome	Dragon-Durey MA;Sethi SK;Bagga A;Blanc C;Blouin J;Ranchin B;Andre JL;Takagi N;Cheong H;Pankaj H;Le M;Niaudet P;Loirat C;Fridman WH;Fremeaux-Bacchi V;	2010	38 children and 8 adults	NR	NR	45 anti-FH positive HUS patients	Abdominal symptoms and diarrhoea were present in 84% and 53% of patients, respectively, which is more frequent than observed in hereditary aHUS (28%). Extra renal complications were frequent: biological hepatitis and pancreatitis were noticed in 50% and 23% of patients, respectively; four patients developed seizures; three cardiac insufficiencies and one diabetes. These complications were rarely reported in hereditary aHUS but were described in 3-10% of Stx-HUS. Outcome was more severe than in Stx-HUS. 7% died after the first flare of the disease, 27% of patients developed End Stage Renal Disease. Relapses occurred in 58% of patients, 39% had chronic renal insufficiency and 25% had no sequel
Haemolytic uremic syndrome (HUS) in children - Follow-up and prognosis	Moczulska A;Zachwieja K;Slowiaczek E;Drozdz D;Ogarek I;Wilkosz K;Stec Z;Kwinta-Rybicka J;Miklaszewska M;Pietrzyk JA;	2010	23 (in 9 atypical D-HUS) Children	NR	NR	children with HUS treated 1996-2009	4/9 D-HUS patients improved without RRT. In D-HUS pts 1 tonsillitis, 1 streptococcal sepsis, 1 varicella, 4 respiratory tract infection were diagnosed. The renal replacement therapy (RRT) was introduced 1,8+/-1,5 days after admission in 16/23 pts (4 HD a. 12 PD).

Title	Author	Publication date	N (children-adult)	Age (median – mean)	Country	Study population	Natural history data
Transplantation in atypical haemolytic uremic syndrome	Riedl M;Hofer J;Rosales A;Yeutukhova Y;Jungraithmayr TC;Zimmerhackl LB;	2010	25	NR	NR	patients with atypical STEC negative HUS.	The data of our registry shows that graft failure due to disease recurrence occurred in more than 50% in the first year of transplantation.
Atypical haemolytic-uremic syndrome:an etiological and clinical analysis of 26 cases	Yu Y;Pei F;Zhao B;Hu Z;	2010	18	NR	NR	patients with atypical haemolytic-uremic syndrome (aHUS) aHUS in our hospital from January 2003 to December 2009	Among the 18 patients who were included in the outcome analysis, 14 achieved complete response and 4 had partial response; 16 had normal renal function, and 2 progressed to ESRD(end stage renal disease
The Haemolytic-Uremic Syndrome	Ramos S;Gomes L;Sarmento A;Faria MS;Costa T;Mota C;Pereira E;	2001	25 Children	NR	Portugal	children with HUS admitted in Nephrology Department of Hospital Maria Pia. from January 1989 to December 2000	In atypical form, two thirds of cases developed complications (50% haematuria, 50% hypertension, 33% proteinuria, 67% end-stage renal failure).
High rate of atypical onset and recurrence in cases of haemolytic uremic syndrome in children	Mir S;Sonmez F;Cura A;Kabasakal C;Basdemir G;	1997	13 ahus pts	Mean age of 9.7 +- 1.2 years	NR	14 patients with HUS were followed between 1984 and 1994	. During the follow-up period, 28 percent of the patients had chronic renal failure, 42 percent had central nervous system involvement and 28 percent had cardiovascular complications. The high rate of recurrence was attributed to the high rate of atypical HUS and advanced age
Clinical aspects of the haemolytic uremic syndrome	Chen CH;Chen WP;Yang LY;Fu LW;Wang HH;Chiou YH;Lin CY;	1998	7	NR	Taiwan	clinical course, complications and outcome of HUS in children	Acute renal failure, hypertension and liver involvement were noted in all cases. Stroke and seizure developed in three of the cases with sequelae. Two cases progressed into end-stage renal disease (ESRD). One case developed acute respiratory distress syndrome (ARDS). Two cases (28.5%) expired. ESRD especially associated with ARDS was highly related to mortality

17.5 Appendix 5: Patient Survey

Please answer the below questions to the best of your ability based on your current situation. You only need to complete the questions that you feel comfortable answering. If you do not wish to answer a particular question, please skip to the next question.

If you are completing this questionnaire on behalf of a child, please answer the questions as best you can on their behalf.

Most of the questions at the beginning of the survey are to be answered by the patient (or by the patient's parent if a child). At the end of the survey there are some questions concerning the impact of aHUS on informal carers/caregivers. If possible, these questions should be completed by the primary carer, but if he or she is not available, then the patient should complete the questions on behalf of the carer, as feasible.

If you have any questions, or need help completing the survey, please contact Adam Hutchings via email at adam@gmasoln.com or via phone at +44 (0) 7545 875817.

Thank you in advance for taking the time to complete this survey. Your time and assistance are greatly appreciated on behalf of patients with atypical haemolytic uraemic syndrome (aHUS) in the UK.

Patient Demographic Information (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

1. How old are you? _____
2. Please indicate whether you are male or female: ___M ___F
3. Please circle your marital status:
    - Married or cohabiting
    - Separated
    - Divorced
    - Widowed
    - Never married
4. Please indicate whether you have children: ____NO ___ YES
5. If "YES", how many children do you have? _____
6. Please circle the highest level of education that you have completed:
    - High school (O-Level / GCSE)
    - College or Sixth Form (A-Levels, NVQ or equivalent)
    - University

- Post graduate or professional qualification

aHUS disease information (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

7. When were you diagnosed with aHUS? (day/month/year) ___/___ /___

8. When was the last time you attended hospital because of your aHUS? (day/month/year) ___/___ /___

9. What was your chronic kidney disease (CKD) stage at your last clinical assessment (please choose from the list below):

    - Stage 0
    - Stage 1
    - Stage 2
    - Stage 3a or 3b
    - Stage 4
    - Stage 5 or End Stage Renal Disease
    - Don't know

10. Are you currently receiving dialysis therapy? _____ NO ___ YES

11. Do you have any current impairment in respect to (please choose from the list below):

    - Neurological impairment?
    - Ophthalmologic (eye) impairment?
    - Cardiovascular (heart) impairment?
    - Renal (kidney) impairment?
    - Other (please specify)
    - No impairments

Impact of aHUS on Employment and School (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

12. Please indicate if you are currently either employed or in education:
_____ NO ___ YES

13. If **"**YES**"** please provide the average number of hours worked or spent in education per week for each entry below that applies to you:

Type of Job or Education	Average number of hours per week
Caregiver for children	

Type of Job or Education	Average number of hours per week
Working in a full time paying job	
Working in a part time paying job	
Self employed	
Volunteer work	
Full time student	
Part time student	
Housework/ home maintenance	

14. If you currently work for pay/profit, or are on sick leave, please circle the category that best describes your main job:
    - Executive, administrator or senior manager
    - Professional
    - Technical support
    - Sales
    - Clerical and administrative support
    - Service occupation
    - Operator or labourer

15. Please indicate what is your annual income from your job, before taxes?
    - £0 - £10,000
    - £10,000 - £20,000
    - £20,000 - £30,000
    - £30,000 - £40,000
    - £40,000 or more

16. If you are currently **not in work** please tick the reason for your situation and record how long you have been in that situation:

Reason for Not Working	How long have you been in this situation?		
	Weeks	Months	Years
Unemployed and looking for work			
Unemployed and unable to work			
Temporarily laid off			
Maternity leave			
Short term sick leave			
Extended sick leave *or* disability			
Retired			

17. Please indicate approximately how many hours you worked in the past seven days?
    - More than 60 hours

- 56 hours
- 40 hours
- 25 hours
- 20 hours
- 10 hours
- Other (please specify):_____

18. During the past seven days, approximately how many total hours did you miss from work or education because of problems associated with aHUS? (Please include all hours you missed as a result of sick days, times you went to work late, left early, etc., because of aHUS.)
    - More than 21 hours
    - 21 hours
    - 8 hours
    - 4 hours
    - Other (specify):_____

19. Please indicate if your income has been reduced due to absenteeism from work as a result of aHUS? ____ NO ___ YES

20. If "YES", please estimate how much your income has been reduced over the last year because of aHUS: £_____

21. Please use the scale below to indicate how much aHUS affected your productivity while you were working or attending school.

    Specifically, please think about days you were limited in the amount or kind of work/school you could do, days you accomplished less than you would have liked, or days you could not do your work/school as carefully as usual. If aHUS affected your work/school only a little, circle a low number on the scale below. Circle a high number if aHUS affected your work/school a great deal.

    Please consider only how much aHUS affected productivity while you were working/in school, not other activities, where 0 equals no effect on activities and 10 equals completely prevented activities.

aHUS had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	aHUS completely prevented me from working

22. Please indicate whether your educational studies have been interrupted because of your disease: _____NO ___ YES

23. Please specify if you receive any of the following payments from the government by entering the amount received per week:

Type of Government Assistance	Amount received per week (£)

Type of Government Assistance	Amount received per week (£)
Jobseekers Allowance	
Income Support	
Incapacity Benefit	
Disability Living Allowance (adult)	
Disability Living Allowance (children)	
Employment and Support Allowance	
Access to Work	
Housing benefit	
Working Tax Credit	
Attendance Allowance	

Impact of aHUS on Non-Work Activities (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

24. Please indicate by circling a number on the scale below, how much aHUS affected your ability to do your regular daily activities, other than attending work or school, over the past seven days?

    By regular activities, we mean the usual activities you do, such as housework, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If aHUS affected your activities only a little, circle a low number on the scale below. Circle a high number if aHUS affected your activities a great deal.

    Please consider only how much aHUS affected your ability to do your regular daily activities, other than work at a job, where 0 equals no effect on activities and 10 equals completely prevented activities.

aHUS had no effect on activities	0	1	2	3	4	5	6	7	8	9	10	aHUS completely prevented my activities

Impact of aHUS on Leisure Activities (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

25. Please indicate by circling a number on the scale below to what extent you were able to take part in leisure activities during the past seven days?

    Please consider only how much aHUS affected your ability to do your leisure activities, where 0 equals no effect on leisure activities and 10 equals completely prevented leisure activities.

aHUS had no effect on my leisure activity	0	1	2	3	4	5	6	7	8	9	10	aHUS completely prevented me from engaging in leisure activities

Home Adaptations Due to aHUS (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

26. Please indicate if you have had to change your housing since being diagnosed with aHUS: _____NO ___ YES

27. If "YES" please indicate the reason you changed housing by circling one of the reasons below:
    - To be closer to a specialist, hospital, or Centre of Expertise
    - To be closer to a relative or other carer
    - To be in more suitable accommodation
    - Other (please specify):_____

Transportation Due to aHUS (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

28. Please indicate how you meet your daily mobility needs by circling the answer that corresponds to your situation:
    - Use own car alone
    - Use own car accompanied by a carer
    - Use public transportation alone
    - Use public transportation accompanied by a carer
    - Use exclusively carer's vehicle
    - Other (please specify):_____

29. Please indicate how many **times a week** you have to travel because of your aHUS (e.g., to attend doctor visits): _____

30. Please indicate approximately **how many hours a week** you have to travel because of your aHUS (e.g., to attend doctor visits): _____

31. Please indicate approximately how much your weekly transportation costs are related to your aHUS (including petrol, car maintenance, buses, train, taxi, etc.): £_____

Out of Pocket Medication/Aids/Therapy Due to aHUS (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

32. Please indicate if you need to pay out of pocket for any medication or therapy (e.g., physiotherapy) as a consequence of your aHUS: _____NO ___ YES

33. If "YES", please specify the weekly amount you have to pay out of pocket for medication or therapy related to aHUS: £_____

34. Please indicate if you need supportive aids to help with your mobility, self-care, or communication, as a result of aHUS? _____NO ___ YES

35. If "YES", please specify the approximate amount spent in the last year on supportive aids: £_____

aHUS Patient Quality of Life (to be completed by patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

36. Please indicate how you assess your overall health status by circling a number on the scale below, where 0 equals the worst imaginable health state and 10 equals the best imagineable health state

Worst imaginable health state	0	1	2	3	4	5	6	7	8	9	10	Best imaginable health state

Carer/Caregiver Support (to be completed by the patient or the patient's parent on behalf of the person with aHUS if he or she is a child)

37. If you receive support from a carer, please indicate the type and the number of hours of care received each week:

Type of Carer	Number of Hours per Week
Informal (non-paid) carer	
Social or health services provided carer	
Charity or voluntary organisation carer	

38. If you receive support from an **informal carer**, please specify the relationship you have with him/ her (circle number):
    - Husband/ Housewife
    - Son/ Daughter
    - Relative (other)
    - Friend
    - Neighbour
    - Other (please specify):_____

Impact of aHUS on informal (unpaid) Carer/Caregiver (to be completed by the carer, or if not available, by the patient on behalf of the carer)

39. As an **informal carer**, lease indicate if you have had to reduce your professional activity to help support the patient: _____NO ___ YES

40. If **"**YES**"** please tick the number of hours you have had to reduce your work per week:
    - Unable to work
    - Reduced more than 25 hours

- Reduced by 20 hours
- Reduced by 15 hours
- Reduced by 8 hours
- Reduced by 4 hours
- Other (specify):_____

Primary Carer Quality of Life

Please think about your experience as a carer within the last two weeks and please tick the box that applies next to each statement.

40. I feel depressed due to caring
    - Never
    - Some of the time
    - A lot of the time
    - Always

41. I feel worn out as a result of caring
    - Never
    - Some of the time
    - A lot of the time
    - Always

42. I am mentally exhausted by caring
    - Never
    - Some of the time
    - A lot of the time
    - Always

43. I am physically exhausted by caring
    - Never
    - Some of the time
    - A lot of the time
    - Always

44. I feel stressed as a result of caring
    - Never
    - Some of the time
    - A lot of the time
    - Always

The following question should be answered by the primary carer in relation to the carer's own health. In the absence of the carer, patients should answer directly on behalf of the carer.

41. Please indicate how you assess your overall health status by circling a number on the scale below, where 0 equals the worst imaginable health state and 10 equals the best imagineable health state

Worst imaginable health state	0	1	2	3	4	5	6	7	8	9	10	Best imaginable health state

17.6 Appendix 6: Physician Survey

The following questions were posed in phone interviews with physician experts in the treatment of aHUS in the UK.

Physician Information [to be requested from respondent in advance of call]

1. Please indicate your specialty.

2. Please indicate your years of experience since completing your medical training?

3. How many patients with aHUS have you treated per year, on average, for last 5 years?

4. How many patients with aHUS have you treated with eculizumab?

5. Do you have any potential conflict(s) of interest to declare, involving eculizumab or aHUS?

aHUS Patient Characteristics

6. What is the average age of the aHUS patients at presentation to the subspecialists who treat aHUS?

7. Describe the “typical” aHUS patient presentation briefly.

8. What is the patient’s CKD stage at presentation to the subspecialists who treat aHUS?

9. What proportion of aHUS patients do you believe may die without ever having been diagnosed? What proportion of aHUS patients do you believe progress to ESRD without ever having been diagnosed?

10. How is the confirmatory diagnosis made?

Current Standard of Care

For the following questions, consider a patient population similar to that described in Legendre et al., 2013, who does not receive eculizumab. Consider both trial populations presented in Legendre et al.

11. What constitutes Standard of Care (excluding eculizumab) in the UK? We consider it to be plasma exchange or infusion, kidney transplant, and dialysis, as needed. Please comment.

[Note, rephrase questions below if plasma infusion indicated as SOC instead of plasma exchange]

12. If plasma exchange is used, how often are the plasma exchange administrations in the first month?

13. How much plasma is exchanged in a given plasma exchange day? Do you follow a guideline, if so which one? (e.g., Clinical Practice Guidelines for the management of Atypical Haemolytic Uraemic Syndrome in the United Kingdom, 2009, Section 5. Management of aHUS; Ariceta et al.)

14. What other resources are consumed during the plasma exchange service? (Refer to the table below, provided by a Canadian expert, with Canadian prices)

Table: Canadian Plasma Exchange Costs (Expert 3)

Annual Plasmapheresis Costs (60 kg patient)	Cost in 2012	Cost per day assuming twice per week plasma exchange	Reference
Central Venous Access Costs (/yr)	$6,273	$52	*
Nursing Costs (2 treatments/week X 4 hours/tx X 36 dollars per hour)	$14,976	$144	Assumption
Plasma Costs ($358/ 250 ml unit x 40 ml/kg x 2 sessions per week)	$376,635	$3,580	**
Other Consumables Costs	$5,000	$48	Assumption
	Total (per PLEX day):	$3,824	

* Manns B, Tonelli M, Yilmaz S, Lee H, Laupland K, Klarenbach S, Radkevich V, Murphy B. Establishment and Maintenance of Vascular Access in Incident Hemodialysis Patients: A Prospective Cost Analysis. J Am Soc Nephrol 16: 201–209, 2005.
** Canadian Blood Services estimate

15. After the first month, how frequently does the patient continue to receive plasma exchange administrations?

16. What other resources, like inpatient days, physician consults, and drugs, are consumed during a six-month course of SOC?

Outcomes on SOC

17. What is the mortality likelihood of the patient in the first year on for patients on dialysis untreated with eculizumab? Our model assumes 5.1% per six months age-adjusted mortality probability, based on the UK Renal Registry 15th Annual Report.

18. What percentage of patients would be ineligible for transplant unrelated to aHUS in the physician survey?

19. For the patients who receive a transplant, what is the likelihood over the next year that the patient dies? Our model assumes 10% in the six months after transplant, based on previous elicited clinical opinion. It should not be lower than ESRD mortality

20. What is the five-year mortality likelihood of the patients on SOC? Is assuming an additional 1.9% per six months reasonable?

21. What is the likelihood (over a six-month period) of a non-fatal, extra-renal TMA event, when a patient is on SOC? Model assumes 11% (i.e., approximately 1 in 5 patients will suffer a TMA event per year)

22. What resources are involved in managing a non-fatal extra-renal TMA event over the six month period beginning with the TMA event?

23. What is the loss in quality of life in a non-fatal TMA event? If "100" were the QoL level of an aHUS patient without a non-fatal TMA event, what would the QoL level of an aHUS patient be who experienced a non-fatal TMA event, over the six month period beginning with the TMA event?

In the eculizumab pivotal trials patients' quality of life increased from baseline to study end. Other than CKD or TMA event mediated improvements, what other benefits from eculizumab do you think account for this improvement?

17.7 Appendix 7: Excel Spreadsheet Containing Economic Model (Section 12)

[redacted]

17.8 Appendix 8: Excel Spreadsheet Containing Budget Impact Model (Section 13)

[redacted]

17.9 Appendix 9: NHS England Policy Statement: Clinical Commissioning Policy Statement: Eculizumab for atypical Haemolytic Uraemic Syndrome

Please see attached PDF included in the submission package.

18 Related procedures for evidence submission

18.1 Cost-consequences models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-

standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who

are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).