Evidence Review Group's Report

Eculizumab for treating atypical haemolytic uraemic syndrome

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

Authors Dr Paul Tappenden, Reader, ScHARR, The University of Sheffield
Ms Alice Bessey, Research Associate, The University of Sheffield
Mr Abdullah Pandor, Senior Research Fellow, The University of Sheffield
Dr Eva Kaltenthaler, Reader, The University of Sheffield
Mrs Anna Cantrell, Information Specialist, The University of Sheffield
Ms Becca Harvey, Research Associate, The University of Sheffield
Dr Kate Ren, Research Associate, The University of Sheffield
Dr Monica Hernandez, Lecturer, The University of Sheffield
Dr Carol Inward, Consultant Paediatric Nephrologist, Bristol Royal Hospital for Children
Professor Moin Saleem, Professor of Paediatric Renal Medicine and Honorary Consultant Paediatric Nephrologist, Bristol Royal Hospital for Children

Correspondence to Dr Paul Tappenden, ScHARR, The University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

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Declared competing interests of the authors and peer reviewers

Dr Anna Richards has spoken at educational meetings on aHUS and renal thrombotic microangiopathies for Alexion Pharmaceuticals. Dr Richards also sat on Alexion's Scottish and Global Advisory Boards for aHUS in 2011-12. Dr Richard's husband, Dr David Kavanagh, is the Kidney Research UK expert nominee and has submitted testimony as part of this NICE HST appraisal. None of the other authors or reviewers have any conflicts of interest to declare.

Previous research outputs relating to eculizumab

Dr Tappenden, Dr Kaltenthaler and Ms Bessey were involved in the AGNSS assessment of eculizumab for aHUS and have published an NIHR-funded peer reviewed systematic review of eculizumab for aHUS based on evidence available in the public domain (BMJ Open, 2013;3).

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Tappenden acted as the project lead and modeller on this assessment; he critiqued the manufacturer's definition of the decision problem, developed the ERG model and undertook additional economic analyses. Alice Bessey helped develop the description of the manufacturer's model, led the critical appraisal of the manufacturer's economic analysis and checked the ERG's exploratory model. Abdullah Pandor and Eva Kaltenthaler critiqued the manufacturer's systematic review of clinical effectiveness evidence. Anna Cantrell critiqued the manufacturer's searches. Becca Harvey and Monica Hernandez critiqued the regression analyses contained within the manufacturer's submission. Carol Inward and Moin Saleem provided clinical advice to the ERG and peer reviewed the draft report. All authors contributed to the writing of the report.

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List of abbreviations

AE	Adverse event
AGNSS	Advisory Group for National Specialised Services
aHUS	atypical haemolytic uraemic syndrome
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BNF	British National Formulary
CI	Confidence interval
CKD	Chronic kidney damage
CNS	Central nervous system
CrI	Credible interval
D+ HUS	Diarrhoea-positive HUS
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
ESRD	End stage renal disease
ESRF	End stage renal failure
FFP	Fresh frozen plasma
HRG	Healthcare resource groups
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
HUS	Haemolytic uraemic syndrome
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LOCF	Last observation carried forward
LOWESS	Locally Weighted Scatterplot Smoothing
LYG	Life year gained
MCP	Membrane cofactor protein
MS	Manufacturer’s submission
MSE	Mean squared error
NHS	National Health Service
n/a	Not applicable
NICE	National Institute for Health and Care Excellence
OLS	Ordinary least squares
ONS	Office for National Statistics

PE/PI	Plasma exchange/infusion
PICO	Population, intervention, comparators, outcomes
PNH	Paroxysmal nocturnal haemoglobinuria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RaDaR	UK Registry for Rare Kidney Diseases
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Standard care
SLE	Systemic Lupus Erythematosus
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TMA	Thrombotic microangiopathy
TTO	Time trade-off
TTP	Thrombotic thrombocytopenic purpura

1. SUMMARY

1.1 Background

Haemolytic uraemic syndrome (HUS) is a disease characterised by thrombotic microangiopathy (TMA), defined by vessel wall thickening and intraluminal fibrin/platelet thrombi that can lead to kidney failure. Clinical features include diarrhoea, often with bloody stool, hence referred to as diarrhoea-positive HUS (D+ HUS). D+ HUS is a self-limiting disease that mostly affects children, and more than 90% of children recover independent renal function. A second type of HUS is a rare form of the disease known as atypical haemolytic uraemic syndrome (aHUS); aHUS may be familial or sporadic, and has a poor prognosis. It has similar clinical features to HUS, although bloody diarrhoea is usually absent and is associated with defective complement regulation. Approximately 10% of HUS cases are identified as being atypical because the cause is not due to infections from *Escherichia coli* or other bacteria. aHUS is a TMA affecting kidney function that can lead to irreversible renal damage as well as non-renal complications. aHUS can occur at any age, from the neonatal period to adult age. Onset during childhood (≤ 18 years) appears slightly more frequent than during adulthood (approximately 60% and 40% of all cases respectively). The majority of children who develop aHUS (70%) will experience the disease for the first time before the age of two years and approximately 25% before the age of 6 months.

There is uncertainty with respect to the number of patients with aHUS in the UK. The manufacturer's submission (MS) quotes an incidence estimate of 5.5 persons per million based on the estimated prevalence in NHS North East. The MS indicates a prevalence estimate of 0.60 persons per million. The MS highlights that there is some uncertainty that all prevalent cases of aHUS have been identified and diagnosed within England.

aHUS has a worse prognosis than HUS with mortality rates ranging from up to 10 to 15% during the acute phase and up to 50% of cases later progressing to end stage renal disease (ESRD). The prognosis for patients with aHUS is partly determined by the underlying complement abnormality. Mutations in the genes coding for CFH, CFI, C3 or thrombomodulin are associated with a worse prognosis. Recent data from the French aHUS registry indicates a better outlook in terms of mortality, with reported rates of 7% and 0.8% at 5-years for children and adults respectively. Rates of ESRD are however high in children and adult patients. aHUS and its treatment may severely impair health-related quality of life (HRQoL).

Traditionally, plasma therapy (plasma exchange and/or plasma infusion) has been the first-line treatment for aHUS based largely upon consensus, as no controlled studies have been performed. Guidelines for the initial therapy of aHUS have been published by the British Transplantation Society

and the European Paediatric Study Group for HUS. These guidelines recommend that plasmapheresis should be initiated within 24 hours of diagnosis of aHUS, and that all patients with aHUS should be offered a trial of plasma exchange and/or plasma infusion. The MS suggests that current treatments for aHUS are ineffective in reducing morbidity and mortality. The MS recognises that transplantation (kidney or liver-kidney) is generally not recommended due to the high risks of graft loss in these patients. The MS does not however fully present outcomes reported within relevant aHUS registry studies. In September 2013, NHS England published a commissioning policy statement detailing arrangements for the provision of eculizumab (Soliris®) for the treatment of aHUS; this is however an interim policy and is intended to provide access to the drug whilst NICE guidance is being developed.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

The MS includes details of a recent aHUS UK sponsored survey which was undertaken with the intention of better understanding the impact of aHUS on patients and their families. Thirty seven patients completed all or part of the survey. This survey highlights the following points:

- aHUS has a substantial impact upon patients' productivity and may impact upon patients' education.
- aHUS may have a substantial impact upon patients' day-to-day activities and participation in leisure activities.
- A proportion of aHUS patients have to move house as a consequence of their disease. Reasons provided included being closer to a specialist centre, being closer to a relative or carer, or moving into a more suitable type of accommodation.
- Patients may require around four hours of travel time per week for activities associated with their aHUS (such as hospital visits).
- aHUS patients may require formal or informal care; this may cause psychological distress for those providing care.

1.3 Critique of the decision problem in the manufacturer's submission

The remit of the appraisal, as specified in the final NICE scope, is to evaluate the benefits and costs of eculizumab within its licensed indication for the treatment of aHUS for national commissioning by NHS England. The ERG notes several deviations from the final agreed NICE scope. Briefly, these include:

- The ERG is not convinced that all available evidence on the comparators in the MS has been systematically identified, quality assessed and the outcomes fully reported (particularly with respect to aHUS registry studies).

- The manufacturer notes that data are not available for some outcomes outlined in the final NICE scope; these include time to disease recurrence and eligibility for/success of transplantation for eculizumab.
- The manufacturer's model includes kidney transplantation and dialysis as a part of the treatment pathway rather than as comparators in their own right. Liver-kidney transplantation is not included in the manufacturer's model.

1.4 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical evidence presented in the MS is based on a systematic review of eculizumab for the treatment of patients with aHUS. Whilst no other scientific evidence was submitted by other consultees, one did provide details of the current interim national service for aHUS implemented by NHS England.

The manufacturer's searches did not identify any randomised controlled trial (RCT) evidence assessing eculizumab against any other comparator for the treatment aHUS. In the absence of RCT evidence, the manufacturer's systematic review identified and included two published (C08-002A/B, C08-003A/B) and two unpublished (interim data from C10-003 and C10-004) prospective studies and one retrospective study (C09-001r). All prospective studies were manufacturer sponsored, phase 2, open-label, non–randomised, single-arm studies that included a diverse range of patients. Study C08-002A/B included aHUS patients (aged ≥12 years) who were resistant to plasma therapy (n=17), whereas study C08-003A/B included aHUS patients (aged ≥12 years) that were plasma therapy sensitive (n=20). The unpublished C10-003 study included children (aged between 1 month to 18 years) with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine (n=22). In contrast, the C10-004 study included adult patients (aged over 18 years) with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine (n=41). In this study there was no requirement for patients to be undergoing plasma therapy. The retrospective observational study included 30 patients (paediatrics, adolescents, and adults) who had been diagnosed with aHUS who received at least one dose of eculizumab between 2007 and 2009 outside of a manufacturer sponsored study.

The prospective efficacy data generally indicate that eculizumab is effective in a diverse range of patients with aHUS. Compared with baseline, improvements were observed in normalisation of platelet count, TMA activity, renal function and quality of life by 26 weeks. Study extension results (median 114 weeks in study C08-002A/B, C08-003A/B; [redacted]) found that the benefits of treatment were sustained. Similar effects were observed by 26 weeks in the retrospective study. Almost every patient in the prospective studies (and

most in the retrospective study) experienced one adverse event; however, not all were considered by the study investigators to be treatment-related. SAEs associated with eculizumab therapy appeared to be uncommon. Three deaths were observed in the prospective (n=1) and retrospective studies (n=2); however, none were deemed by the study investigators to be related to eculizumab. Similarly, three reports of meningococcal infection with eculizumab treatment in aHUS patients have been reported in prospective (n=2) and retrospective (n=1, post market report) studies.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the manufacturer is not comprehensive because it is neither transparent nor reproducible. Despite limitations in the manufacturer's search strategy, the ERG is confident that all relevant studies were included in the MS (including details of ongoing studies); however, this may not be the case for the comparator studies as no proper attempt was made to search for these. The specified inclusion and exclusion criteria are (mostly) appropriate and generally reflect the information given in the decision problem. However, published case series (and case studies) were excluded from the review. Despite the inherent biases associated with this study type, the inclusion of such evidence in the systematic review may have increased the evidence base and strengthened the credibility of the review. The validity assessment tool used to appraise the prospective studies was based on the quality assessment criteria for RCTs. However, as the included studies were not RCTs, it is unclear why other more relevant tools were not used.

Although the efficacy and safety of eculizumab was positively demonstrated (compared with baseline) in the included studies, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the absence of a control group in all four prospective eculizumab studies, inference of treatment effects (including magnitude) may be confounded. Similarly, due to the absence (or clear presentation) of a systematic review of the efficacy and safety of relevant comparators (e.g. plasma therapy, dialysis or transplantation) within the MS, outcome differences cannot be compared against the comparators specified in the NICE scope. In addition, AEs deemed to be treatment-related were identified by the study investigators (no details were available on whether safety outcomes were also assessed by an independent endpoint assessment adjudication committee) and as such may have been open to bias. The key uncertainties in the clinical evidence relate to optimal dosing and duration of treatment. There are no well controlled long-term prospective studies of eculizumab therapy and therefore it is unclear whether all patients need to continue long-term therapy.

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The MS includes the details of a systematic review of economic evaluations of eculizumab for the treatment of aHUS. The manufacturer did not identify any economic evaluations studies of eculizumab for aHUS. The ERG does however note that a previous appraisal of eculizumab by the Advisory Group for National Specialised Services (AGNSS) has been undertaken and the methods and results of a health economic model developed by the manufacturer to inform this appraisal are available online. This information is not however presented within the relevant sections of the MS. The ERG believes that this model and its results should have been discussed by the manufacturer within their review.

The MS includes a *de novo* quality-adjusted life year (QALY) based cost-consequence model to assess eculizumab versus standard care for the treatment of patients with aHUS from the perspective of the NHS. This model was made available to the ERG. The model uses a Markov structure to estimate the costs and consequences for a 28-year old aHUS population over a lifetime horizon, discounted at a rate of 1.5%. The model simulates the experience of patients with aHUS receiving eculizumab or standard care principally in terms of the progression of kidney damage (defined as severity of chronic kidney disease [CKD]) and its impact in terms of costs, HRQoL and survival. CKD transition probabilities were derived from the treatment phase and pre-treatment phase of two prospective eculizumab studies (C08-002A/B and C08-003A/B). Other parameter values were derived from registry reports, standard costing sources and the wider literature. The manufacturer's economic analysis includes a number of simple sensitivity analyses and probabilistic sensitivity analysis (PSA).

The manufacturer's model suggests that given a discount rate of 1.5%, eculizumab produces an estimated 24.08 additional years of life and 25.22 additional QALYs compared to standard care per patient. The discounted incremental cost of eculizumab versus standard care is estimated to be approximately [redacted] per patient. The manufacturer's simple sensitivity analyses indicate that the estimates of incremental health benefit and incremental cost are particularly sensitive to assumptions about patient age and the discount rate.

1.7 Summary of the ERG's critique of the value for money evidence submitted

The ERG noted several problems with the manufacturer's economic analysis. These include: (i) concerns regarding the scope of the manufacturer's economic analysis; (ii) problems relating to the derivation of transition matrices for eculizumab and standard care; (iii) highly favourable assumptions for the benefits of eculizumab; (iv) use of a restrictive model structure; (v) inappropriate handling of competing risks; (vi) inappropriate estimation of background mortality; (vii) inappropriate use of

probabilistic sampling and use of deterministic model results; (viii) use of a conceptually unclear model population; (ix) pooling of potentially heterogeneous study populations, and; (x) the presence of several technical modelling errors. Overall, the ERG has concerns regarding the suitability of the model structure, the integrity of the pre-model analysis and the robustness of the manufacturer's model results.

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The MS includes the details of a budget impact model which is used to estimate the total costs to the NHS for the period 2013 to 2017. The analysis presented by the manufacturer suggests that without eculizumab, the absolute cost of treating patients with aHUS is between £6.4million and £7.1million each year. Based on the manufacturer's analysis, the net budget impact of recommending eculizumab is estimated to be approximately [redacted] in 2013, rising to [redacted] in 2017. The overall 5-year predicted net budget impact will be around [redacted] over the period 2013-2017.

The MS also includes estimates of the impact of eculizumab on (i) lost productivity, government benefits and tax revenues for patients and current/ex carers of aHUS patients, (ii) estimates of cost savings associated with out-of-pocket expenditures for patients and carers including, transportation, housing and other costs; and (iii) other carer costs. Based on the analysis undertaken by the manufacturer, the largest cost-saving is expected to result from lost productivity avoided.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

The ERG notes that the estimates of uptake for eculizumab within the budget impact analysis appear to be low. Assuming 100% uptake, the budget impact model predicts a 5-year net budget impact of in excess of [redacted] over the period 2013 to 2017.

The ERG also believes that the manufacturer's estimates of non-health benefits are substantially over-estimated due to the inclusion of inappropriate resource items (e.g. transfer payments) and the use of unrealistic assumptions within the analysis. Furthermore, since the manufacturer's societal analysis does not consider the non-health benefits forgone associated with curtailing existing treatments and services to fund eculizumab, the ERG does not believe that this analysis is helpful in informing decision-making.

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

The ERG notes the following strengths of the MS:

- The MS contains relevant information relating to the retrospective and prospective studies of eculizumab for the treatment of patients with aHUS.
- The MS contains details of a recent UK survey sponsored by aHUS UK which provides relevant information concerning the impact of the disease on patients and their families.
- The MS includes details of a systematic search that was used to identify RCT and non-RCT evidence of eculizumab for aHUS.
- The MS includes a range of economic information including a QALY-based cost-consequence model, an assessment of the expected costs to the NHS and an assessment of wider societal (non-health) benefits associated with recommending eculizumab.

The ERG notes the following weaknesses of the MS:

- The ERG is confident that all relevant studies of eculizumab were included in the MS; however, it is not entirely clear if all relevant comparator studies were identified or included. Relevant outcomes data for the specified comparators have not been systematically or transparently reported. Additional evidence in the form of case series (and case studies) was also identified; however, these data were excluded from the manufacturer's review.
- The clinical evidence base for eculizumab is restricted to non-randomised studies with very small sample sizes. The primary endpoints within these studies are intermediate outcomes. There is no direct comparative evidence relating to the benefit of eculizumab versus standard care in terms of long-term patient-relevant outcomes (survival and HRQoL).
- The manufacturer's model suffers from a number of errors. Further, the credibility of the outcomes for patients receiving standard care are questionable, as relevant registry data have not been used to inform the modelled prognosis of patients receiving standard care. The ERG does not believe that the results of the model can be considered robust.
- The manufacturer's budget impact analysis appears to underestimate the likely uptake of eculizumab following a positive recommendation.
- The manufacturer's analysis of wider societal (non-health) benefits includes several inappropriate items and unrealistic assumptions. The analysis does not consider the expected cost-savings lost due to the displacement of other technologies and services in order to fund eculizumab.

A number of uncertainties exist within the current evidence base for eculizumab:

- *Comparative benefits of eculizumab versus standard care.* There are currently no direct head-to-head randomised studies of eculizumab versus any other active comparator. All of the clinical

evidence relating to eculizumab presented in the MS takes the form of single-arm studies. Whilst the MS mentions the existence of comparative data from registry studies, this evidence has not been reviewed or reported in a systematic fashion.

- *Long-term patient-relevant outcomes of eculizumab and standard care.* The prospective and retrospective studies of eculizumab discussed in the MS are relatively short-term and focus on intermediate endpoints. Whilst these endpoints are clinically relevant, their translation to longer-term patient-relevant outcomes (e.g. survival) is subject to considerable uncertainty.
- *Comparative HRQoL benefits of eculizumab versus standard care*. The available evidence on the impact of eculizumab on patients' HRQoL may be subject to confounding as it is drawn from single arm studies which did not include a control group. The incremental HRQoL benefits of eculizumab versus standard care remain at best, highly uncertain.
- *Effectiveness and costs of eculizumab in paediatric patients.* The evidence base for paediatric populations is comparatively weaker than that for the adult population. Ongoing eculizumab studies may help to elucidate the effectiveness of eculizumab in younger patients.
- *Optimal treatment and frequency strategy.* There remains uncertainty with respect to the optimal treatment strategy using eculizumab. There exists no published evidence on alternative dosing to that described in the license or on the use of intermittent treatment to manage flares. As aHUS may follow a relapsing/remitting type of disease course for some patients, continual use of eculizumab may not be necessary once the patient has stabilised (the same is true of plasmapheresis in a proportion of patients). There is also some evidence that patients with certain genetic abnormalities have a better prognosis than others. It should also be noted that indefinite treatment using eculizumab requires fortnightly infusions which will present a burden for some patients. Future research should consider the careful balance of risks and benefits of alternative treatment strategies using eculizumab. Ideally, such research should take the form of randomised controlled trials.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG.

The ERG undertook two additional sets of analyses: (1) a more detailed exposition of the design and outcomes of the registry studies mentioned in the MS, and; (2) the development of a new exploratory model which resolves the errors identified in the manufacturer's model and allows for the inclusion of registry data to model prognosis and outcomes for patients receiving standard care.

Examination of the registry studies mentioned in the MS indicates a wider range of relevant outcomes than those presented by the manufacturer. The aHUS-specific registry data reported by Fremeaux-Bacchi *et al* suggest that at 5-years, 7% of paediatric patients died and 29% reached ESRD, whilst 0.8% of adults died and 63% reached ESRD. The aHUS-specific registry data reported by Noris *et al*

suggest that at 3-years, 11% of patients had died whilst 45% had reached ESRD. These estimates suggest that the manufacturer's model may substantially over-estimate the mortality risk for patients with aHUS receiving standard care.

The ERG model suggests that given a discount rate of 3.5% for costs and health outcomes, eculizumab is expected to produce 10.14 additional QALYs compared against standard care at an additional discounted cost of [redacted]; this estimated discounted cost is higher than the equivalent value generated by the manufacturer's model ([redacted]). The incremental QALY gained is markedly lower than the estimate submitted by the manufacturer; this difference is driven principally by the use of aHUS registry data to model the prognosis and outcomes of patients receiving standard care within the ERG model.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of aHUS and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Review Group (ERG) and information presented in the background sections of the manufacturer's submission (MS).[1] For additional details regarding the aetiology, epidemiology, health impact, diagnosis and treatment of aHUS, please refer to the MS (pages 20-58).

2.2 Description of health problem

2.2.1 Haemolytic uraemic syndrome

Haemolytic uraemic syndrome (HUS) was first described in 1955[2] and is recognised as the most common cause of acute renal failure in the paediatric population. It is a disease characterised by thrombotic microangiopathy (TMA), defined by vessel wall thickening and intraluminal fibrin/platelet thrombi that can lead to kidney failure. The disease begins with signs of enteritis, generally caused by verocytotoxin secreting bacteria strains[3] particularly the *Escherichia coli* 0157 strain which release toxins, specifically Shiga toxins. The toxins produced by the bacteria damage the blood vessels that line the kidney. Clinical features include diarrhoea, often with bloody stool, hence referred to as diarrhoea-positive HUS (D+ HUS). D+ HUS is a self-limiting disease that mostly affects children, and more than 90% of children recover independent renal function.[4] A second type of HUS is a rare form of the disease known as atypical haemolytic uraemic syndrome (aHUS). aHUS may be familial or sporadic, and has a poor prognosis. It has similar clinical features to HUS, although bloody diarrhoea is usually absent and is associated with defective complement regulation. The first mutations in a gene that predisposes patients to the development of aHUS were identified in 1998.[5]

2.2.2 Atypical haemolytic uraemic syndrome

Approximately 10% of HUS cases are identified as being atypical[6,7] because the cause is not due to infections from *Escherichia coli* or other bacteria. aHUS is a TMA affecting kidney function that can lead to irreversible renal damage as well as non-renal complications. It is associated with prescription medications (ovulation inhibitors, immunosuppressive agents), diseases (malignancies, systemic lupus erythematosus [SLE]) and pregnancy.[8] A defect in the regulation of the complement cascade accounts for approximately half of all cases of aHUS. aHUS can occur at any age, from the neonatal period to adult age and is equally frequent in males and females when onset occurs during childhood.[9] However, when arising in adults, aHUS affects females more frequently than males.[10] Onset during childhood (≤ 18 years) appears slightly more frequent than during adulthood (approximately 60% and 40% of all cases respectively).[11,12] The majority of children who develop aHUS (70%) will

experience the disease for the first time before the age of two years and approximately 25% before the age of 6 months.[9]

2.2.3 Epidemiology

aHUS is a rare disease with varying figures on its reported incidence and prevalence. The prevalence of aHUS in children, estimated from European community data (France, Germany, Austria and Italy), is approximately 7 cases per million. aHUS can be familial and around 20% of cases are inherited from family members. There remains uncertainty with respect to the number of patients with aHUS in the UK. The 2011 Alexion submission to AGNSS reported that in 2011 there were approximately 139 patients with a diagnosis of aHUS in England, however, applying estimates derived from the North East of England to the rest of England would suggest that this is an underestimate by a factor of approximately 2.[13] Equivalent updated figures for 2013 are not presented in the manufacturer's submission to the National Institute for Health and Care Excellence (NICE),[1] although the MS does quote an estimated incidence estimate of 5.5 persons per million, again based on the estimated prevalence in NHS North East. Worldwide, the prevalence of aHUS is thought to be between 2.7 and 5.5 per million population, with an incidence of about 0.40 per million population.[14] The MS[1] indicates a higher prevalence estimate of 0.60 per million persons, although the source of this figure is unclear. The MS states that according to aHUS clinical experts in the UK, there is still some uncertainty that all prevalent cases of aHUS have been identified and diagnosed within England.[1]

2.2.4 Aetiology

aHUS is a condition that develops due to dysregulation of the alternative complement activation pathway.[15] The alternative pathway of complement is part of the innate immune system that does not require antibodies to trigger an immune response. It includes plasma and membrane-bound proteins that protect the body against invading organisms and is the main system for defence against bacteria. This pathway is in a continual low-grade state of activation generating C3b, which binds indiscriminately to pathogens and host cells; in aHUS this activity becomes excessive, particularly along the renal glomerular and arteriolar endothelial and basement membranes. Mutations leading to functional abnormalities of complement or complement regulatory factors are found in more than 50% of patients with aHUS.[16] The mechanism by which dysregulation of the alternative pathway of complement leads to complement-mediated TMA is not clear, but microangiopathy probably results from chronic uncontrolled production of complement activity, mediated through (C5a and C5b9) at the endothelial surface. A trigger leads to a loss of endothelial cell integrity, causing activation of pro-coagulation pathways and development of TMA.[17] Excessive complement activation may be due to either a failure to adequately prevent complement activation on host tissue due to 'loss of function' in the complement regulatory genes that control the amplification, or feedback loop of the alternative

complement pathway, or excessive complement activation on glomerular endothelium due to 'gain of function' mutation in complement activating genes.[17]

Four alternative pathway regulatory proteins are implicated in the dysregulation of the alternative complement activation pathway ([1] Factor H; [2] membrane cofactor protein (MCP or CD46); [3] Factor I, and; [4] thrombomodulin), and two proteins of the C3 convertase-factor B and C3.[18] Further detail regarding the current understanding of the mechanism of the disease is presented in the MS.[1]

2.2.5 Pathogenesis

Several causative agents have been identified including nonenteric infections, viruses, drugs, malignancies, transplantations, and pregnancy. *Streptococcus pneumoniae* accounts for nearly 40% with a less favourable short-term course and good recovery on a long-term basis compared with other types of aHUS.[7,11] An infectious event, most commonly an upper respiratory tract infection or diarrhoea/gastroenteritis, triggers the onset of aHUS in at least half of all patients.[4] Although aHUS is delineated from HUS by the absence of diarrhoea, it has been observed that diarrhoea preceded aHUS in 23% and 28% of patients in the French paediatric cohort[9] and the Italian adult and paediatric cohort,[11] thus indicating that post-diarrheal onset does not eliminate the diagnosis of aHUS. Microvascular endothelial injury leads to microthrombi. Fragmented red blood cells result from abnormally high levels of shear stress produced as blood flows through turbulent areas of the microcirculation e.g. kidneys that are partially occluded by platelet and fibrin thrombi.[17]

2.2.6 Clinical features

Young children typically present with a sudden onset of the illness, with pallor, general distress, poor feeding, vomiting, fatigue, drowsiness and sometimes oedema. Adults may also complain of fatigue and general distress. In addition, central nervous system (CNS) involvement occurs in about 10% of patients with drowsiness, seizures, diplopia, cortical blindness, hemiparesis or hemiplegia, stupor, or coma.

In about 20% of children, the onset of aHUS progresses over several weeks or months and manifests with subclinical anaemia and fluctuating thrombocytopenia without renal dysfunction.[9] The illness may then go into remission, followed by an acute relapse, or patients may develop progressive hypertension and proteinuria that may induce nephrotic syndrome over several weeks or months.[18] Myocardial infarction due to cardiac microangiopathy has been reported in approximately 3% of patients.[11,19] Approximately 5% of patients develop a life-threatening multivisceral failure due to diffuse TMA, with CNS manifestations, cardiac ischemic events, pulmonary haemorrhage and failure, pancreatitis, hepatic cytolysis and intestinal bleeding.[9,11]

2.2.7 Diagnosis

The diagnosis of aHUS is difficult where there is no family history of the disease. The diagnostic criteria associated with aHUS are haemolytic anaemia (anaemia in the presence of broken red blood cells), low platelet count (thrombocytopenia) and severe kidney lesions in a patient with minimal or no diarrhoea without bloody stools. aHUS is considered genetic when two or more members of the same family are affected by the disease at least six months apart and exposure to a common triggering infectious agent has been excluded, or when a disease-causing mutation(s) is identified in one of the genes known to be associated with aHUS, irrespective of familial history.

Differentiation of classical HUS and aHUS is important for both treatment and outcome, as patients with aHUS have historically required plasmapheresis with replacement by fresh frozen plasma (FFP).[6] Familial occurrence of aHUS is reported in siblings, in a few families with autosomal dominant inheritance and rarely with autosomal recessive transmission.[20] In some families, affected individuals exhibit decreased plasma levels of C3, indicating defective complement control and supporting a role of complement regulators for the disease process.[10,11]

2.2.8 Prognosis

aHUS has a worse prognosis than HUS with mortality rates of up to 10 to 15% during the acute phase and up to 50% of cases later progressing to end stage renal disease (ESRD).[20] The prognosis for patients with aHUS is partly determined by the underlying complement abnormality.[11] Mutations in the genes coding for CFH, CFI, C3 or thrombomodulin are associated with a worse prognosis. Overall, three years after the first episode of aHUS, an estimated 53% of familial cases and 37% of sporadic cases result in end stage renal failure (ESRF) or death.[11] Recent data from the French aHUS registry indicate a better outlook in terms of mortality, with a reported mortality rate of 8% and 1.6% at 5-years for children and adults respectively. However, reported rates of ESRD are consistently high in children and adults.

2.2.9 Impact on patients' health-related quality of life (HRQoL)

The MS[1] indicates that renal and non-renal manifestations of aHUS are associated with significant impairment of quality of life for patients through frequent and severe morbidities, including renal impairment and the impact of aHUS on other vital organs.[1] The MS cites renal damage, CNS symptoms, gastrointestinal symptoms, cardiac symptoms and pulmonary symptoms as key factors affecting patients' HRQoL. The MS also suggests that aHUS patients may not overtly exhibit clinical symptoms at all times, although patients' normal activities may be impaired after treatment and some patients may also experience psychological trauma as a consequence of fear of relapse and the anticipation of requiring re-initiation of treatment.[1] Evidence relating to the overall impact of aHUS

and current standard treatments on HRQoL within the MS is limited. Quality of life data for patients receiving eculizumab are presented in the MS and are detailed in Chapters 4 and 5 of this report.

In 2013, aHUS UK sponsored a UK survey with the intention of better understanding the impact of aHUS on patients and their families (see MS[1] page 38). Thirty seven patients completed all or part of the survey. This survey highlights the following main points:

- aHUS has a substantial impact upon patients' productivity and may impact upon patients' education.
- aHUS may have a substantial impact upon patients' day-to-day activities and participation in leisure activities.
- A proportion of aHUS patients have to move house as a consequence of their disease. Reasons provided included being closer to a specialist centre, being closer to a relative or carer, or moving into a more suitable type of accommodation.
- Patients may require around four hours of travel time per week for activities associated with their aHUS (such as hospital visits).
- Several aHUS patients require formal or informal care; this may cause psychological distress for those providing care.

2.3 Current service provision

2.3.1 Plasma exchange/infusion

Plasma therapy has traditionally been the first-line treatment for aHUS based largely upon consensus, as no controlled studies have been performed. Guidelines for the initial therapy of aHUS have been published by the British Transplantation Society[4] and the European Paediatric Study Group for HUS.[21] The European Consensus Guidelines recommend that plasmapheresis should be initiated within 24 hours of diagnosis of aHUS,[21] and the UK guideline recommends offering all patients with aHUS a trial of plasma exchange and/or plasma infusion.[4] The rationale for such treatment is that plasma exchange removes mutant complement proteins (CFH, CFI, CFB, C3 and anti-CFH antibodies) responsible for the disease, and introduces normal levels of CFH, CFI, CFB and C3, while restitution of fresh frozen plasma restores the functional proteins.

Response to plasma therapy is variable and results are partly dependent on the gene mutation present in patients. Renal function may continue to deteriorate after plasma therapy with progression to ESRF or death in most patients with CFH, CFI, THBD gene, or C3 defects.[11] Better response to plasma therapy has occurred in patients with MCP mutations, although patients with this mutation often recover with or without plasma therapy[11] and therefore in retrospective analysis their response to plasma therapy appears better. However, the mutation is often unknown when aHUS is first

diagnosed and patients may be receiving plasma therapy prior to identification of mutated genes. Nevertheless, patients may have additional gene mutations e.g. CFI where plasma therapy is beneficial. In patients with no identifiable abnormality of the complement proteins or where no anti-CFH antibodies can be detected, around 50% of patients progress to ESRF or death within 3 years from onset despite plasma therapy.[11]

The MS[1] recognises that a large proportion of patients do not have an identifiable genetic mutation, but does not include due consideration of differential prognoses of patients with particular genetic abnormalities.[1] This is important information which may be of relevance in identifying which patients would benefit most from eculizumab.

2.3.2 Kidney transplantation

Renal transplantation has been associated with a high rate of recurrence in aHUS patients. The risk of post-transplant recurrence of aHUS depends on the genetic abnormality involved, and ranges from 15% to 20% in patients with mutations in the gene that encodes membrane cofactor protein and from 50% to 100% in patients with mutations in the genes that encode circulating regulators and activators of complement. Overall recurrence rates are reported to be 100% for patients with CFB mutations, 75%-90% for patients with CFH mutations, 45% to 80% for patients with CFI mutations, and 40%-70% for patients with C3 mutations.[22]

Better response to renal transplantation has occurred in patients with gene mutations for MCP, with 15% to 20% experiencing graft failure. Reports suggest that plasma therapy administered after recurrent post-transplant aHUS has in general failed to prevent graft loss, although most cases are not reported and its therapeutic role is unclear. The prophylactic administration of plasma therapy administered before and after renal transplantation was reported to prevent recurrent aHUS in 8 renal transplant recipients, including patients with mutations in CFH, CFI, and C3 genes.[22] Therefore, identifying the genetic defect in patients with aHUS helps to inform treatment options and prognosis.

2.3.3 Combined liver-kidney transplantation

A US consensus conference[23] held in 2007 produced treatment guidelines for aHUS. This consensus statement recognises that isolated kidney transplantation is unlikely to be successful and a combined liver-kidney transplant is recommended for those with Factor H mutations, if transplantation is to be undertaken. However, transplantation remains a high risk experimental procedure with little evidence to support its use. The guidelines recognise that the risks associated with the procedure have not been eliminated completely, and recommends that the assessment of risk and benefit are carefully

considered. The use of liver-kidney transplants for the treatment of aHUS in the UK remains limited and empirical evidence of efficacy is limited to small case series.

Overall, the MS suggests that current treatments for aHUS are ineffective in reducing morbidity and/or mortality, stating that 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.[1] As noted in Chapters 3 and 4, the ERG believes that useful data are available from aHUS-specific registries and that the manufacturer has not reported these outcomes data systematically or transparently.

2.4 Description of the technology under assessment

2.4.1 Eculizumab

Eculizumab (Soliris®) is a humanised monoclonal IgG2/4κ antibody produced from murine myeloma cells by recombinant DNA technology. It is a complement inhibitor that binds specifically to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a, (a pro-thrombotic and pro-inflammatory molecule), and C5b, (preventing the generation of the terminal complement membrane attack complex, C5b-9). In aHUS, impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy. Eculizumab is intended for the first-line treatment of patients with aHUS. It is administered intravenously at 1,200mg every 2 weeks as maintenance therapy in adolescents and adults, and 300-900mg every 2 or 3 weeks for paediatric patients depending on body mass (see Table 1). Maintenance treatment would be used continuously for the rest of a patient's life, unless the discontinuation of the drug is clinically indicated.[24] Life-threatening and fatal meningococcal infections can occur in patients treated with eculizumab and patients are required to receive immunisation with a meningococcal vaccine at least 2 weeks prior to administering the first dose of eculizumab.

Table 1: Eculizumab dosing regimen

Body mass	Induction dose	Maintenance dose
Patients < 18 years of age		
5kg to <10kg	300mg weekly x 1 dose	300mg at week 2; then 300mg every 3 weeks
10kg to <20kg	600mg weekly x 1 dose	300mg at week 2; then 300mg every 2 weeks
20kg to <30kg	600mg weekly x 2 doses	600mg at week 3; then 600mg every 2 weeks
30kg to <40kg	600mg weekly x 2 doses	900mg at week 3; then 900mg every 2 weeks
≥ 40kg	900mg weekly x 4 doses	1200mg at week 5; then 1200mg every 2 weeks
Patients ≥ 18 years of age		
	900mg weekly x 4 doses	1200mg at week 5; then 1200mg every 2 weeks

The British National Formulary (BNF) lists the following side-effects for eculizumab: gastro-intestinal disturbances; oedema; cough, nasopharyngitis; headache, dizziness, fatigue, dysgeusia, paraesthesia; infection (including meningococcal infection); spontaneous erection, dysuria; arthralgia, myalgia; blood disorders (including thrombocytopenia); alopecia, pruritus, rash; influenza-like symptoms; infusion-related reactions; less commonly anorexia, gingival pain, jaundice, palpitation, haematoma, hypotension, chest pain, syncope, hot flushing, epistaxis, anxiety, depression, mood changes, sleep disturbances, Graves' disease, menstrual disorders, renal impairment, malignant melanoma, muscle spasms, myelodysplastic syndrome, visual disturbances, tinnitus, hyperhidrosis, petechiae, and skin depigmentation.[25]

2.5 Current usage in the NHS

Eculizumab received marketing authorisation from the European Medicines Agency (EMA) for the treatment of paediatric and adult patients with aHUS in September 2011.[24] According to the MS,[1] eculizumab has also been granted marketing authorisation for the treatment of aHUS in the following countries:

- United States (September 2011)
- Israel (December 2011)
- Switzerland (May 2012)
- Australia (November 2012)
- Canada (March 2013)
- Colombia (June 2013)

Eculizumab was launched in the UK in November 2011. One 30mL (300mg) vial of eculizumab (concentrate for intravenous infusion) currently costs £3,150.00.[25] For patients over 12 years of age or with a body mass greater than or equal of 40kg, this corresponds to an annual acquisition cost of approximately £342,279 per patient including induction and subsequent maintenance therapy, or approximately £329,649 per patient for maintenance therapy only. Eculizumab also holds a full EMA marketing authorisation for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).[24]

In 2011, the Advisory Group for National Specialised Services (AGNSS) commissioned an appraisal of the clinical effectiveness and cost-effectiveness of eculizumab for the treatment of aHUS. As part of this appraisal, Alexion submitted a dossier of evidence relating to eculizumab for the treatment of aHUS.[13] This dossier was examined and critiqued by an independent Evidence Review Group (ERG); the authors of the ERG report prepared for AGNSS[26] are also the authors of this ERG report to NICE. In June 2012, AGNSS recommended to ministers that eculizumab should be commissioned nationally

for the treatment of English patients with aHUS. The summary recommendation from AGNSS is presented in Box 1.

Box 1: AGNSS' 2012 recommendation to the NHS on the use of eculizumab for aHUS[27]

"AGNSS recommended to ministers that eculizumab should be commissioned nationally for the treatment of English patients with atypical haemolytic uraemic syndrome (aHUS). AGNSS also recommended that The Newcastle upon Tyne NHS Hospitals Foundation Trust should be designated as the expert centre to provide care for these patients, employing shared care where possible, supported by telemedicine. The Department of Health and the NHS Commissioning Board should take steps to negotiate the cost of eculizumab as the numbers of patients diagnosed with aHUS rises and any new indications are identified."

Whilst the Government accepted the advice of AGNSS with respect to the clinical effectiveness of eculizumab in treating aHUS, further advice was requested with respect to its suitability for direct commissioning taking account of its cost, benefit and affordability. Subsequently, the Government asked NICE to develop guidance on the use of eculizumab in its treatment of aHUS as the first topic in its new Highly Specialised Technologies Programme.[28]

In September 2013, NHS England published a commissioning policy statement detailing arrangements for the provision of eculizumab for the treatment of aHUS; this is however an interim policy and is intended to provide access to the drug whilst NICE guidance is being developed. The NHS commissioning statement is presented in Box 2.

Box 2: NHS England interim commissioning policy statement for eculizumab in the treatment of aHUS[29]

NHS England will commission eculizumab for new patients with atypical haemolytic syndrome (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.

The MS notes that given that the NHS England policy statement is very recent, its impact on the uptake of eculizumab within the NHS in England has yet to be fully seen.[1]

3. CRITIQUE OF THE MANUFACTURER'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope,[30] is to evaluate the benefits and costs of eculizumab within its licensed indication for the treatment of aHUS for national commissioning by NHS England. The final NICE scope[30] outlines the agreed population, intervention, comparators and outcomes for the appraisal. The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

3.2 Adherence to the decision problem

Table 2 presents a summary of the decision problem as set out in the NICE scope[30] and the manufacturer's adherence to this (based on information presented on pages 21-22 of the MS[1]). It should be noted that the table presented within the MS differs slightly from the factors included in the final NICE scope.

Table 2: Adherence of the MS to the agreed decision problem

Component	Final scope issued by NICE	Deviations of submission from the scope
Population	Children and adults with atypical haemolytic uraemic syndrome (aHUS)	The clinical evidence relates to children and adults with aHUS. However, the cost-consequence analysis submitted by the manufacturer relates only to the costs and health outcomes for an adult population.
Intervention	Eculizumab (Soliris®)	The intervention is in line with scope.
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	The MS notes that there is no variation between the scope and the submission although current data do not allow the relevant information to be presented in the distinct groups/format detailed in the NICE scope. The ERG does not believe that available evidence on the comparators has been systematically identified, quality assessed and the outcomes associated with these have not been fully or transparently reported. The submitted cost-consequence model compares eculizumab against a general comparator referred to as "standard care" and is assumed by the manufacturer to include plasma therapy. Kidney dialysis and transplantation are assumed to reflect part of the pathway and are not evaluated as comparators in their own right. Liver-kidney transplantation is not considered within the manufacturer's cost-consequence model.
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	The manufacturer notes that data are not available for some outcomes outlined in the scoping document; these include time to disease recurrence and eligibility for/success of transplantation for eculizumab. Whilst RCTs do not exist for eculizumab versus any other comparator, non-randomised evidence has been identified and reviewed systematically for eculizumab. The same is not true for the comparators specified within this appraisal. The ERG suggests that the consideration of outcomes, and more generally prognosis, for patients receiving the comparators defined in the NICE scope should have been identified and reported in a more comprehensive and systematic manner (see Section 4.4).

Component	Final scope issued by NICE	Deviations of submission from the scope
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	The manufacturer states that there are no variations from the final scoping document. The ERG agrees that evidence relating to the nature of the condition has been considered and included within the MS. Alongside descriptions of the clinical and pathophysiological aspects of the disease, the submission also includes non-scientific information relating to a sponsored survey of UK aHUS patients facilitated by the UK aHUS Patients and Families Support Group, as well as recent newspaper articles summarising experiences for patients with aHUS and quotes from patients and their families in support of a National Specialised Service for eculizumab for the treatment of aHUS.
Cost to the NHS and PSS, and value for money	• budget impact in the NHS and PSS, including patient access agreements (if 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)	The manufacturer states that there is no variation from the final scoping document and the ERG broadly agrees with this. The submission includes a QALY-based cost-consequences model to estimate the lifetime costs and health outcomes associated with eculizumab versus standard care. This is in line with the interim NICE methods and process guide for highly specialised technologies. The manufacturer's cost-consequence model estimates costs and QALYs; this information could be synthesised to address questions of technical efficiency, and to some degree, allocative efficiency, by comparing whether the additional health gains associated with eculizumab outweigh the health forgone associated with curtailing existing services. As noted on page 132 of the MS, the manufacturer has not undertaken an incremental cost-effectiveness analysis. The MS also includes a related budget impact model which predicts the costs to the NHS of providing eculizumab for the treatment of aHUS over a five-year time period, from the beginning of 2013 to the end of 2017.

Component	Final scope issued by NICE	Deviations of submission from the scope
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.	The manufacturer states that there is no variation from the final scoping document. The MS indicates that the proposed commissioning of eculizumab and potential development of a service based on centres 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). The MS also notes that manufacturer is sponsoring an international aHUS registry that will capture and continue to follow aHUS patients irrespective of treatment status. Currently, very few English patients have been recruited into this registry. In addition, the MS reports an analysis of wider societal (non-health) benefits associated with the use of eculizumab. This analysis includes estimates of (i) lost productivity, government benefits and tax revenues for patients and current/ex carers of aHUS patients, (ii) cost-savings associated with out-of-pocket expenditures for patients and carers including, transportation, housing and other costs; and (iii) other carer costs.
Other considerations	None	No deviation from the scope.

3.3 ERG critique of the manufacturer's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the clinical sections of the submission relates to adults and children with aHUS. [redacted]. The brief consideration of comparators within the MS includes some data from TMA/aHUS registries (Noris *et al,*[11] Coppo *et al,*[31] Fremeux-Bacchi *et al*[32] and Hovinga *et al*[33]); however, some of these registries include patients who do not have aHUS. The MS does not consider differential effectiveness or costs of eculizumab for patients in whom a specific genetic abnormality can be identified.

3.3.2 Interventions

The intervention included within the MS relates to eculizumab in line with its licensed indication. It should be noted that as part of the clarification process, the manufacturer highlighted some minor dose discrepancies in the prospective eculizumab studies and [redacted] in the retrospective eculizumab study. In these instances, the available evidence may not strictly adhere to the EMA licensed indication.[24]

3.3.3 Comparators

The ERG believes that evidence relating to the effectiveness of the comparators specified in the NICE scope is given insufficient attention within the MS. Whilst the manufacturer purports to have undertaken a systematic review which identified no randomised controlled trials, they have only explicitly reported the outcomes of a review of prospective and retrospective single-arm studies of eculizumab (several issues regarding the manufacturer's review methods are discussed in Chapter 4). The same approach is not used to detail outcomes data for the comparators specified in the NICE scope.[30] During the clarification process (response to question #1) the manufacturer stated:

"We did in fact provide a systematic review of standard of care (SOC) interventions in our September 2013 submission; however, the information is not included in one location or specific section. Specifically, we reviewed four thrombotic microangioapthy (TMA)/HUS registries available in the literature that identified and followed a large number of aHUS patients. The results of these registries are described in the following publications: Caprioli et al 2006, Noris et al 2010, Hovinga et al 2010, and Coppo et al 2010." [34]

The MS does not however include details with respect to how the registry studies were identified, how they were selected, the methodological quality of these studies, or the range of relevant outcomes data reported within the source publications. This is a major weakness of the MS which limits the interpretation of the full range of available evidence.

3.3.4 Outcomes

The range of outcomes reported within the MS differs for eculizumab and the comparators. Whilst the outcomes data for eculizumab are handled in a generally systematically fashion, the same is not true of the comparators specified in the NICE scope; instead the MS reports general figures for adverse consequences of aHUS across a selection of registry studies.

(a) Outcomes reported for eculizumab (note - not all outcomes are reported in all studies)

- Change in platelet count from baseline
- Normalisation of platelet count
- Complete TMA response
- TMA event-free status
- TMA intervention rate, pre-eculizumab/during eculizumab treatment
- Chronic Kidney Disease (CKD) improvement
- Estimated glomerular filtration rate (eGFR), change from baseline
- eGFR improvement ≥ 15 mL/min/1.73m2
- Decrease in proteinuria by ≥ 1 grade
- HRQoL
- Hb improvement
- Hematologic normalisation
- New dialysis event free status
- PE/PI event-free status
- CKD improvement by at least one stage after initial dose (target day 7)
- Complete TMA response with preservation of renal function
- Modified complete TMA response with improvement renal function
- CKD improvement by at least one stage at 4 weeks (target day 28)
- New dialysis event-free status
- PE/PI event-free status

(b) Outcomes reported for standard care (note - discussion of these outcomes is based on a general interpretation of registry data but is not presented separately for individual studies)

- Percentage of patients reaching ESRD or death at certain timepoints
- Graft loss
- Incidence of neurological complications, cardiac complications and gastrointestinal complications

Other potentially relevant information is available concerning the prognosis of patients receiving the comparator treatments, however this is not adequately detailed in the MS (e.g. disaggregated ESRD/mortality outcomes at different timepoints, remission rates following plasma therapy). This evidence is further discussed in Chapter 4.

3.3.5 Cost to the NHS and PSS, and value for money

The MS includes a cost-consequence model in which the primary health outcome is valued in terms of incremental QALYs gained. The manufacturer's model does not use any of the aforementioned evidence from the aHUS registries to characterise progression of chronic kidney damage but instead uses data from the pre-treatment phase of prospective eculizumab studies C08-002A/B and C08-003A/B. These issues are discussed and explored in detail in Chapters 5 and 6 of this report.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The MS[1] includes a systematic review of published and unpublished evidence of eculizumab for the treatment of patients with aHUS. A detailed critique of the methods of the review is presented in this chapter. The ERG notes that the systematic review process followed by the manufacturer is not comprehensive and is neither transparent nor reproducible. This should be borne in mind when interpreting the results presented within this chapter.

4.1.1 Searches

Several aspects of the searches for clinical evidence undertaken by the manufacturer were confusing. Information concerning the searches is provided in the main body of the submission (see MS[1] pages 59-65, Section C9,[1] and Appendix 17.1.4, pages 218-220). However, there are inconsistencies between these two sections. The manufacturer clarified that Table C1 (MS pages 60-61) contained the correct search terms used to identify the clinical evidence (see response to clarification questions[34] #13).

The population, intervention, comparators and outcomes (PICO) is not discussed in the search section but the search does have terms for the population and intervention aspects of PICO. In Table C1 (see MS[1] pages 60-61), an attempt was made to use an exhaustive list of terms for the aHUS facet of the search. Wildcards could have been beneficially added to include the British and North American spellings. For the intervention, eculizumab, the name of the licensed drug Soliris® and the CAS registry number are not included; the use of these alternative terms for eculizumab would have made the search more comprehensive. Boolean logic is utilised to combine all the terms for the population and intervention using the OR term (see MS[1] Table C1 pages 60-61, search string 7, Medline and Embase search). In order to retrieve evidence on eculizumab for the treatment of patients with aHUS, it would have been more appropriate to combine the population terms (search strings 1-4) using the OR term and then combine this with the intervention terms (search string 5) using the AND logic term. Appropriate Boolean logic is used in step 8 to ensure that RCTs are retrieved. The searches provided in the MS did not include any terms for the comparators of eculizumab e.g. plasma infusion, plasma exchange, dialysis or renal transplant. Whilst it is possible that the aforementioned search strategy may have retrieved studies on the comparator treatments, it cannot be guaranteed that all relevant comparator studies have been identified as no proper attempt was made to search for these. Whilst free-text terms were used in the Medline, Embase and Cochrane library search strategy, it is unclear whether subject headings or thesauri terms were used in these searches. Translation of the search strategies from the Medline database to the Cochrane Library (Table C1 (see MS[1] pages 60-61) was inconsistent with fewer terms used for the search in the Cochrane library.

Initially it was difficult to determine what date and language limits were applied to the searches (see MS[1] pages 59-61 and Appendix 17.1.4); however, the manufacturer clarified that the searches were limited to humans, English Language and publication year 2000-current (see response to clarification questions[34] #14). The "human" limit is justified and potentially the "2000-current" limit appears to be acceptable due to the evolving nomenclature and understanding of aHUS and other TMA-related diseases. The justification for limiting studies to the English language to identify the publications most likely to be relevant to the English setting is less convincing. The most substantial problem with limiting a systematic review to English language only studies is that it can lead to publication bias. Additionally, the evidence base for eculizumab is small therefore any evidence, even if not directly applicable, could be considered important.

Only two terms were used to retrieve RCTs (see MS[1] Table C1, pages 60-61). A sensitive filter could have been used to increase the sensitivity of the search. Additionally, the submission states that due to the lack of high quality evidence in the form of RCTs, extra terms were added in order to find non-RCT evidence. A number of study types are then listed; however, it is unclear how these terms were used in the search (see MS[1] page 63). The manufacturer's response in request to clarification failed to conclusively answer how these terms were used (see response to clarification question[34] #15).

A range of databases was searched for the clinical evidence although information about the service provider was not included (see MS[1] Appendix 17.1.1). It was unclear from the description of the search in the MS whether Medline In-Process had been searched. The manufacturer clarified that Medline in Process was searched within Embase. If the manufacturer had access to Medline it is strange that the In-Process subset was searched within Embase. The ERG notes that the Embase database does not contain all Medline records. Moreover, it is unclear why a larger range of databases was searched to identify economic evidence. A search of Web of Knowledge for the clinical evidence would have beneficially retrieved conference proceedings. Unpublished studies were identified by searching the manufacturer's database of sponsored clinical trials and a clinical trials register (see MS[1] page 60). However, it is not clear if other grey literature sources were searched (e.g. conference proceedings, grey literature databases [OpenSIGLE, The National Technical Information Service], specialist research organisations, professional societies and the World Wide Web) particularly for studies not sponsored by the manufacturer.

4.1.2 Inclusion criteria

Comprehensive and explicit descriptions of the inclusion and exclusion criteria are essential for a systematic review so that the methods and procedures are transparent and reproducible. The inclusion

and exclusion criteria for the systematic review were not clearly specified in the MS[1] (pages 59-66). A summary developed by the ERG, based on the information reported in MS, is provided in Table 3.

Table 3: Inclusion and exclusion criteria in the manufacturer's systematic review

Inclusion criteria	*Population* Adults or children with aHUS *Intervention* Eculizumab *Comparator* Supportive care or placebo *Outcome* Overall survival, response to treatment, avoidance of dialysis, avoidance of plasma therapy, maintenance or improvement of kidney function, other major non-renal clinical outcomes, development of antibodies and resistance, and safety *Study design* Randomised controlled trials (other study designs were considered in the absence of randomised trial evidence)
Exclusion criteria	Patients with typical or acquired HUS Non English language papers

The specified inclusion and exclusion criteria are (mostly) appropriate and generally reflect the information given in the decision problem; however, there appear to be some irregularities in the MS.

Given the absence of RCT evidence identified by their searches, the manufacturer amended the inclusion criteria to include the following study types: retrospective trials, cohort study, case series, case reports and registry data (see MS[1] page 63). Following this amendment, the MS (page 69) and the response to clarification questions[34] (see question #17) stated that published case series (and case studies) were excluded from the review *"due to their wide variability of dose protocol and treatment duration that is inconsistent with the SmPC and the proposed use of eculizumab for aHUS in England."* The ERG notes that despite the inherent biases associated with this study type, the inclusion of such evidence in the systematic review may have increased the evidence base and strengthened the credibility of the review.[35] The inclusion of such study designs may also have allowed for the exploration of issues around the optimal dosing, frequency and treatment duration in future studies of eculizumab.

In the MS (page 59), the comparator was considered to be supportive care; however, a clear and explicit description was lacking in the systematic review. After seeking further clarification, the manufacturer highlighted that supportive care included plasma exchange or plasma infusion, chronic

dialysis or kidney transplantation (see MS[1] page 31). It is noteworthy that the decision problem (see Chapter 3, Table 2) proposed two distinct patient groups for supportive care and included plasma infusion and/or plasma exchange therapy in newly diagnosed people who have not received prior treatment and kidney dialysis or kidney/liver transplantation in previously treated people with kidney impairment.

Although adults and children with aHUS were the population of interest, it would have been beneficial if the disease of interest was defined using explicit criteria e.g. how the disease is defined, how the disease of interest is verified, how studies involving only a subset of relevant participants will be handled and which participants were excluded. Similarly, a clear and explicit description of the outcomes for the systematic review would have been beneficial. Nevertheless, the ERG considers the manufacturer's outcome selection to be relevant and appropriate.

Finally, as noted in the previous section, limiting a systematic review to English language only studies can lead to publication bias.

4.1.3 Critique of data extraction

The MS[1] (pages 60 and 221) provides a brief description of the study selection process; however, it is unclear if a parallel independent assessment was conducted to minimise the risk of errors and selection bias. In addition, the MS does not provide any details relating to the data extraction process (e.g. which information was extracted from the included studies, if authors of primary studies were contacted to provide missing or additional data and if more than one researcher extracted the data). The use of standardised data extractions forms, with data extractions being independently checked, reduces potential bias and improves validity and reliability of a systematic review.

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in MS (page 87) was based on the quality assessment criteria for RCTs as suggested by the NICE guideline template for manufacturers. However, it is not clear whether the critical appraisal process was undertaken by a single reviewer or consensus of multiple reviewers.

After seeking further clarification from the manufacturer on the appropriateness of an RCT appraisal tool to critically appraise non-randomised studies of eculizumab, the manufacturer claimed (see response to clarification questions[34] #18) that *"an alternative template was not identified that would provide a similar appraisal as the…RCT template."* The ERG considers the use of an RCT methodological assessment tool to be inappropriate as the included studies were not RCTs (see MS[1]

pages 87-91). Moreover, Deeks *et al*.[36] have identified over 180 tools for assessing the quality of non-randomised studies of interventions. It is unclear why one of these more relevant tools was not used.

4.1.5 Evidence synthesis

The manufacturer did not undertake a formal meta-analysis as this was considered to be inappropriate due to the diversity of the clinical and methodological characteristics of the included studies (see MS[1] page 109). As a result, the manufacturer undertook a narrative synthesis of the evidence; no explicit details were provided on how this approach was undertaken. Ideally, a narrative synthesis approach should be pre-specified, justified, rigorous (i.e. describe results without being selective or emphasising some finding over others) and transparent to reduce potential bias.[37,38] Despite the lack of transparency, the ERG acknowledges that the narrative synthesis approach undertaken by the manufacturer was acceptable.

4.2. Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The manufacturer's PRISMA flow diagram relating to the literature searches (see MS[1] pages 62 and 64) is confusing and does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/statement.htm). In addition, the MS does not provide a full and explicit breakdown of the reasons why all citations were rejected, especially after full text papers were retrieved for detailed evaluation.

As no RCTs were identified in the MS, the systematic review included four manufacturer sponsored, prospective studies (C08-002A/B, C08-003A/B, C10-003 and C10-004) and one retrospective study (C09-001r) as the main supporting evidence for the efficacy and safety of eculizumab in the treatment of patients with aHUS. Two additional ongoing observational studies were also identified: C11-003 and M11-001. A summary of the study designs and population characteristics at baseline within these studies is provided in Tables 4 and 5. It is noteworthy that despite the manufacturer stating that a systematic review of standard care was undertaken (see response to clarification questions[34] #1) there is no transparent evidence of this in Section C of the MS (pages 59-119). For example, no details were provided for the following: number of studies included for the systematic review of standard care, quality assessment of included studies and no presentation or synthesis of results from included studies. However, the ERG acknowledges that selective reporting of results from several registries is provided in the MS, albeit in several sections which are not particularly relevant to the systematic review (page 31 [Section B - Nature of condition], 128 [Section C 10.1.16 – appears to be a comment] and 139 [Section D – Value for money and cost to the NHS…], MS).

Table 4: Summary of design characteristics (MS[1] pages 28-29, 69-80)

Study	Country (sites)	Design	Number of treated patients (enrolled)[a]	Intervention	Duration	Primary outcome	Study status type of report
Prospective studies							
C08-002 A/B	Austria, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, UK, and the USA, (74 study sites across 30 centres)	Phase 2, open-label, non-randomised, single arm study	17 (17)	Eculizumab fixed dose schedule: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	26 weeks; patients allowed to continue in long-term extension until product registered and available	Reduction of TMA measured by change in platelet count from baseline and haematologic normalisation	Enrolment and primary endpoint complete; Clinical Study report complete; extension trial on-going; published report Legendre *et al*. 2013[39]
C08-003 A/B	Austria, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, UK, and the USA (69 study sites across 30 centres)	Phase 2, open-label, non-randomised, single arm study	20 (23)	Eculizumab fixed dose schedule: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	26 weeks; patients allowed to continue in long-term extension until product registered and available	Reduction of TMA measured by TMA event-free status and haematologic normalisation	Enrolment and primary endpoint complete; Clinical Study report complete; extension trial on-going; published report Legendre *et al*. 2013[39]
C10-003	[redacted]	Phase 2, open-label, non-randomised, single arm study	22 (NR)	Eculizumab fixed dose, multiple weight-based dosing regimens.	26 weeks; patients allowed to continue in extension until product registered and available	Complete TMA response confirmed by 2 consecutive measurements	Enrolment and primary endpoint complete; [redacted] Unpublished

Study	Country (sites)	Design	Number of treated patients (enrolled)[a]	Intervention	Duration	Primary outcome	Study status type of report
C10-004	[redacted]	Phase 2, Open-label,non-randomised, single arm study	41 (NR)	Eculizumab fixed dose schedule: 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	26 weeks; patients allowed to continue in extension until product registered and available	Complete TMA response confirmed by 2 consecutive measurements	Enrolment and primary endpoint complete; [redacted] Unpublished
Retrospective studies							
C09-001r	Multi-national (no further details provided)	Retrospective, chart review	30 (30)	Eculizumab; Variable dosing schedule (no further details provided)	Variable no further details provided)	Reduction in TMA as measured by change in platelet count from baseline, TMA event free status and difference in TMA intervention rates	Study complete; Clinical Study Report Complete. Published as abstract[40] and additional data in the EMA assessment report[41]
Ongoing studies							
C11-003	Multi-national (no further details provided)	Phase IV observational, long term follow up study	Data not available	[redacted]	[redacted]	TMA complication-free survival	Ongoing
M11-001	Multi-national (no further details provided)	Observational registry	Data not available	[redacted]	[redacted]	Various	Ongoing; baseline abstract submitted

[a] Data for the number of enrolled patients was obtained from the EMA Assessment Report for Eculizumab[41] as the MS did not provide this information (including the number of patients screened)

Table 5: Summary of patient characteristics at baseline

Characteristic	Prospective studies				Retrospective study
	C08-002A/B	**C08-003A/B**	**C10-003**	**C10-004**	**C09-001r**
Population characteristics					
Description	Adult and adolescent patients with short-duration aHUS (plasma therapy resistant)	Adult and adolescent patients with a long duration of aHUS and chronic renal impairment (plasma therapy sensitive)	Paediatric patients with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine	Adult patients with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine	Any patients with aHUS treated outside of a manufacturer-sponsored study
Demographic characteristics					
Age, years (median, [min; max])	28 (17; 68)	28 (13; 63)	[redacted]	[redacted]	12 (0.17; 51.4)
Age category					
Infant (<2 years)	0	0	[redacted]	0	5
Children (≥2 to 12 years)	0	0	[redacted]	0	10
Adolescent (≥12 to ≤18 years)	1	5	[redacted]	0	4
Adult (≥18 years)	16	15[a]	[redacted]	41	11
Sex (n, %)					
Male	5 (29%)[b]	8 (40)[b]	[redacted]	[redacted]	14 (47%)[c]
Female	12 (71%)[b]	12 (60%)[b]	[redacted]	[redacted]	16 (53%)[c]
Patients with genetic mutation or auto-antibody (n, %)	13 (76%)[b]	14 (70%)[b]	[redacted]	[redacted]	14 (47%)[c]
aHUS disease history					
Time from aHUS diagnosis to screening, months (median, [min; max])	9.7 (0.26; 236)	48 (0.66; 286)	0.56 (0.03; 191.3)[d]	0.79 (0.03; 311.26)	10.9 (0.23; 175.9)[e]
Patients with prior renal transplant (n, %)	7 (41%)[b]	8 (40%)[b]	[redacted]	[redacted]	11 (37%)[c]
First presentation of aHUS (n, %)	7 (41%)[b]	5 (25%)[b]	[redacted]	[redacted]	12 (40%)[c]
aHUS exacerbation history					
Time from current clinical presentation of aHUS to screening, months (median, [min; max])	0.8 (0.2; 3.7)[b]	8.6 (1.2; 45.0)[b]	[redacted]	[redacted]	[redacted]
Number of plasma therapy sessions per patient during	17 (2; 37)[f]	62 (20; 230)	[redacted]	[redacted]	8 (0; 29)

Characteristic	Prospective studies				Retrospective study
	C08-002A/B	**C08-003A/B**	**C10-003**	**C10-004**	**C09-001r**
current aHUS event (median, [min; max])					
Number of plasma therapy sessions per patient within 7 days to first eculizumab dose (median, [min; max])	6 (0;7)[c]	1.5 (1;3)[c]	[redacted]	[redacted]	[redacted]
Patients with dialysis before first eculizumab dose (n, %)	6 (35%)	2 (10%)	11 (50%)	24 (59%)	11 (37%)
Other variables					
Platelet count at baseline($x10^9$/L)					
Median (min; max)	118 (62; 161)	218 (105; 421)	[redacted]	[redacted]	159 (25; 381)
LDH at baseline				[redacted]	
Median (min; max)	269 (134; 634)	200 (151; 391)	[redacted]	[redacted]	[redacted]
Estimated GFR (mL/min/1.73m^2) at baseline					
Median (min; max)	19 (5; 59)[b]	28 (6; 72)[b]	[redacted]	[redacted]	[redacted]
<15 (n, %)	7 (41%)[b]	4 (20%)[b]	[redacted]	[redacted]	8 (27%)[c]
15-29 (n, %)	5 (29%)[b]	6 (30%)[b]	[redacted]	[redacted]	5 (17%)[c]
30-44 (n, %)	4 (24%)[b]	6 (30%)[b]	[redacted]	[redacted]	8 (27%)[c]
45-59 (n, %)	1 (6%)[b]	2 (10%)[b]	[redacted]	[redacted]	3 (10%)[c]
≥60 (n, %)	0[b]	2 (10%)[b]	[redacted]	[redacted]	6 (20%)[c]
Number of patients by CKD stage [c]					
Stage 0	0	0	[redacted]	[redacted]	0
Stage 1	0	0	[redacted]	[redacted]	4 (13%)
Stage 2	0	2 (10%)	[redacted]	[redacted]	2 (7%)
Stage 3a	1 (6%)	2 (10%)	[redacted]	[redacted]	3 (10%)
Stage 3b	4 (24%)	6 (30%)	[redacted]	[redacted]	8 (27%)
Stage 4	5 (29%)	6 (30%)	[redacted]	[redacted]	5 (17%)
Stage 5	7 (41%)	4 (20%)	[redacted]	[redacted]	8 (27%)

GFR, glomerular filtration rate
[a] The MS suggest 23 patients; however, the ERG assumes this is a typographical error
[b] Data from Legendre et al.[39]
[c] Data from EMA Assessment report for eculizumab[41]
[d] duration of confirmed disease
[e] At first dose
[f] Within 56 days of first dose
[redacted]

Studies C08-002A/B and C08-003A/B

The MS[1] did not provide a clear and transparent description of studies C08-002A/B and C08-003A/B (pages 28, 69-74). Additional information was derived from the original published paper reported by Legendre *et al*.[39]

Studies C08-002A/B and C08-003A/B were published multi-centre, single-arm studies conducted in adults (aged >18 years) and adolescent (aged between 12 to 18 years) patients. All patients received meningococcal vaccination at least 14 days before the initiation of eculizumab treatment or received prophylactic treatment with antibiotics until 2 weeks after vaccination. Patients received a fixed-dose schedule of eculizumab with the first dose administered 1 to 6 hours after their most recent plasma therapy session. Eculizumab was given intravenously at a dose of 900mg per week for 4 weeks (induction phase), a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks thereafter (maintenance phase). Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600mg before plasma infusion or within 1 hour after the completion of each plasma exchange. The studies were designed for eculizumab to be administered for 26 weeks with additional treatment available through an extension phase. Each study had two primary endpoints. The first primary endpoint included the inhibition of TMA (indicated by a change in platelet count from baseline) in study C08-002A/B and TMA event-free status for at least 12 weeks (defined as no decrease in platelet count of >25%, no plasma exchange or infusion and no initiation of dialysis) in study C08-003A/B. The second co-primary endpoint in both studies was the proportion of patients who achieved haematologic normalisation (defined as normalisation of both platelet count [>150 $x10^9$/L] and lactate dehydrogenase sustained for at least two consecutive measurements which span a period of least for four weeks). To confirm an eculizumab treatment effect, pre-treatment data were used as within-patient controls. Neither study included a separate control group without exposure to eculizumab.

Study C08-002A/B included patients (n=17) in the early phase of aHUS (median time from diagnosis to screening, 9.7 months) with evidence of progressive TMA after four or more sessions of plasma exchange or infusions (i.e. plasma therapy resistant) in the week before the start of study treatment and impaired renal function. In these patients eculizumab is expected to control the TMA process, prevent progression of TMA and reverse kidney damage. It is noteworthy that 16/17 patients (94%) received PE/PI and 5/17 patients (29%) were receiving dialysis prior to initiation of eculizumab. In addition, two out of 17 patients (12%) received PE/PI during the study. One of these two patients discontinued the study before starting PE (patient was exited from the study because of a protocol violation); the other patient received 17 plasma

exchanges without interrupting eculizumab treatment (see response to clarification questions[34] #5).

In contrast, study C08-003A/B included patients (n=20) with longer term aHUS (median time from diagnosis to screening, 48 months) who had chronic renal impairment, without apparent evidence of clinical TMA and were receiving plasma therapy (exchange/infusion) for a median duration of 10 months prior to study entry (i.e. plasma therapy sensitive). In these patients eculizumab is expected to control the TMA process despite discontinuation of plasma therapy and maintain kidney function. It is noteworthy, all patients (20/20; 100%) received PE/PI and 2/20 patients (10%) were receiving dialysis prior to receiving eculizumab. In addition, one patient (5%) received a single dose of PE/PI without interrupting eculizumab treatment during the study (see response to clarification questions[34] #5).

Studies C10-003 and C10-004 (MS[1] pages 29, 74-77, 112-114)

Despite the limited information in the MS, studies C10-003 and C10-004 were unpublished, multi-centre, single-arm studies conducted in adults (aged >18 years) and paediatric (aged between 1 month to 18 years) patients. All patients received vaccination for *Neisseria meningitidis*, pneumococcal infections, and *Haemophilus influenzae* at least 14 days before the initiation of eculizumab treatment or protected by prophylactic antibiotics. However, the ERG notes that this appears to be slightly different to the guidelines in the SmPC[24] which recommends that all patients must be vaccinated for *Neisseria meningitides* but only recommends vaccination (essential) against *Haemophilus influenzae* and pneumococcal infections in patients less than 18 years of age. The studies were designed for eculizumab to be administered for 26 weeks [redacted]. The primary endpoint in both studies was a complete TMA response defined as haematological normalisation (based on platelet count and lactate dehydrogenase levels) and ≥25% improvement in serum creatinine from baseline confirmed by two consecutive measurements obtained at least four weeks apart.

Study C10-003 included paediatric patients (n=22) with a clinical diagnosis of aHUS (newly diagnosed, existing diagnosis, or post-transplant) exhibiting thrombocytopenia, haemolysis and elevated serum creatinine. Patients that received plasma therapy more than five weeks prior to enrolment or chronic dialysis were excluded.[42] Patients received eculizumab according to a fixed dose, weight-based dosing regimen. Although no study specific details were provided, the ERG assumes that this is based on a fixed-dose weighting schedule as indicated in the SmPC[24] and the MS[1] (pages 24-25). In these patients eculizumab is expected to control TMA as characterised by thrombocytopenia, haemolysis and renal impairment. It is noteworthy that 10/22 patients (45%)

received PE/PI prior to entering the study and 11/22 patients (50%) were receiving dialysis at the time of initiation of eculizumab. [redacted] (see response to clarification questions[34] #5).

Study C10-004 included adult patients (n=41) with a clinical diagnosis of aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine. There was no requirement for PE/PI or dialysis prior to initiating eculizumab therapy. Patients who received chronic dialysis were excluded from the study.[43] Patients received a fixed-dose schedule of eculizumab. This was given intravenously at a dose of 900 mg per week for 4 weeks (induction phase), a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks thereafter (maintenance phase). In these patients eculizumab is expected to control TMA as characterised by thrombocytopenia, haemolysis and renal impairment. It is noteworthy that 36/41 patients (88%) received PE/PI prior to eculizumab treatment and 24/41 (59%) patients were receiving dialysis at the time of initiation of eculizumab. [redacted].

Study C09-001r (see MS[1] pages28, 77-78, 84)

Despite the limited information provided in the MS,[1] study C09-001r was a retrospective chart review of 30 patients that included infants (<2 years), children (2-12 years), adolescents (>12 to <18 years) and adults (>18 years) who had been diagnosed with aHUS and received at least one dose of eculizumab between 2007 and 2009 outside of a manufacturer sponsored study.[44] The dosing schedule and treatment duration were variable (no further details were provided). The primary outcome included a reduction in TMA as measured by change in platelet count from baseline, TMA event-free status and difference in TMA intervention rates (pre-treatment and during treatment).

Ongoing studies (see MS[1] page 29, 78-80)

The MS identified two ongoing observational studies. Study C11-003 is a long-term follow-up study[45] designed to assess the long-term efficacy and safety of eculizumab in patients with aHUS who have previously participated in an eculizumab study [redacted]. The estimated date of study completion (i.e. clinical study report finalisation) [redacted] (see response to clarification questions[34] #51).

The M11-001 aHUS registry[46] is designed to capture post-marketing safety data on patients treated with eculizumab and to collect information on the progression of disease in all aHUS patients receiving eculizumab. Although this is an open registry, the MS and clarification response did not provide any further details of planned data analysis and subsequent publication.

4.2.2 Details of relevant studies not included in the submission

Whilst the ERG is confident that all relevant studies were included in the MS, including details of ongoing studies, the ERG is not convinced that all relevant citations for each of the included studies have been fully reported in the submission (pages 80-83). For example, independent searches conducted by the ERG, based on a search strategy previously developed for the AGNSS assessment of eculizumab for aHUS,[26] identified several citations that were not referenced in the MS, particularly those related to the following subgroups: with or without transplant,[47-49] and with or without history of dialysis.[50] However, the MS[1] (pages 85-86) does provide details of subgroup analyses undertaken and a clear statement of findings, including those with prior kidney transplant and dialysis.

4.2.3 Summary and critique of manufacturer's analysis of validity assessment

The manufacturer provided a formal appraisal of the validity of the included prospective eculizumab studies based on a methodological assessment tool for RCTs (see MS[1] pages 87-91). As noted in Section 4.1.4, the ERG considers the use of an RCT methodological assessment tool to be inappropriate as the included studies were not RCTs. To this end, a risk of bias assessment of the prospective studies (C08-002A/B, C08-003A/B, C10-003 and C10-004) was undertaken by the ERG using a modified methodological assessment tool developed by Chambers *et al.* for non-randomised studies.[35] A key strength of this tool is that it addresses both quality of reporting and risk of bias (principally selection and attrition bias). A summary of the risk of bias in the prospective studies is presented in Table 6.

Table 6: ERG's methodological quality assessment of included prospective studies

Criteria used for quality assessment	C08-002[39]	C08-003[39]	C10-003 (p74-75, 86-87, 98-99, MS)	C10-004 (p75-77, 86-87, 99-101, MS)
1. Were selection/eligibility criteria adequately reported?	Unclear	Unclear	[redacted]	[redacted]
2. Was the selected population representative of that seen in normal practice?	Unclear	Unclear	[redacted]	[redacted]
3. Was an appropriate measure of variability reported?	Yes	Yes	[redacted]	[redacted]
4. Was loss to follow-up reported or explained?	Yes	Yes	[redacted]	[redacted]
5. Were at least 90% of those included at baseline followed up?	Yes	Yes	[redacted]	[redacted]
6. Were patients recruited prospectively?	Unclear	Unclear	[redacted]	[redacted]
7. Were patients recruited consecutively?	Yes	Yes	[redacted]	[redacted]
8. Did the study report relevant prognostic factors?	Yes	Yes	[redacted]	[redacted]

Selection criteria were reported in all studies; however, patient eligibility was not clearly described. Despite an ERG clarification request, the manufacturer (see response to clarification questions[34] #6) failed to provide clear and explicit details on how patients were identified for recruitment into studies C08-002, C08-003, C10-003 and C10-004 or whether all patients identified with aHUS who fitted the inclusion criteria were included in the studies. However, it did state that all study participants were recruited consecutively and enrolled by the investigator at his/her respective study site. As expected in an ultra-rare disease study, not all open study sites identified aHUS patients during the study enrolment period. In addition, it is unclear whether study populations derived from multiple multinational specialist centres can be considered representative of patients with aHUS seen in routine clinical practice. One study restricted the population to include patients aged between 1 month and 18 years (C10-003), two studies restricted the population to include patients aged over 12 years (C08-002A/B and C08-003A/B) and one study included all patients over 18 years of age (C10-004). Despite a broad age range of included patients in the four studies, prospective efficacy and safety data of eculizumab are limited in aHUS patients under 18 years of age (e.g. total data for infants <2 years, [redacted]; children ≥2 to 12 years, [redacted]; adolescents ≥12 to ≤18 years, [redacted] and adults ≥18 years, n=72).

Appropriate measures of variability were used in all studies, with confidence intervals reported around point estimates to indicate variability. Loss to follow-up and reasons for leaving the studies early were reported in all studies, and more than 90% of those included at baseline were followed up. All primary analyses were appropriately analysed using the intention-to-treat (ITT)

population, and missing data was imputed by the last observation carried forward (LOCF) method. It is not explicitly clear from the study reports whether patients were recruited prospectively. Prognostic factors such as complement abnormalities and biochemical tests were reported for all studies. No details were available on adherence rates to the protocol-specified doses of eculizumab therapy. After seeking further clarification (see response to clarification questions[34] #8), the manufacturer noted that adherence data were not available at present for the published C08-002A/B and C08-003A/B studies, whereas data for the C10-003 and C10-004 studies were not accessible as the results were based on interim analyses.

The methodological quality assessment of study C09-001R was not assessed by the ERG due to the inherent biases associated with retrospective study designs. For completeness, the completed validity assessment tool, as reported in the MS (page 91), is reproduced in Table 7.

Table 7: Critical appraisal of observational study C09-001r (MS[1] page 91)

Study name	**C09-001r**	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
1. Was the cohort recruited in an acceptable way?	Yes	[redacted]
2. Was the exposure accurately measured to minimise bias?	Yes	[redacted]
3. Was the outcome accurately measured to minimise bias?	Yes	[redacted]
4. Have the authors identified all important confounding factors?	Yes	[redacted]
5. Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	[redacted]
6. Was the follow-up of patients complete?	N/A	[redacted]
How precise (for example, in terms of confidence interval and *p*-values) are the results?	Yes	[redacted]

4.2.4 Summary and critique of results

This section presents the results (as reported by the manufacturer) from four manufacturer-sponsored, single-arm prospective studies (C08-002A/B, C08-003A/B, C10-003 and C10-004) and one retrospective study (C09-001r) as the main supporting evidence for the efficacy and safety of eculizumab in the treatment of patients with aHUS. Note that data have been re-tabulated in a consistent and more transparent format by the ERG.

4.2.4.1 Efficacy

Due to the variations in (some) outcomes and definitions between studies, a summary of the key results from the published (C08-002A/B and C08-003A/B) and unpublished (interim results: C10-003 and C10-004) prospective studies are reported separately in Tables 8 and 9. Data have been re-tabulated in a consistent and more transparent format by the ERG. It is noteworthy, that a number of discrepancies were identified in the reported data, particularly between sections reported in the MS[1] and between the MS[1] and the published paper by Legendre *et al.*[39] Where applicable, these discrepancies have been highlighted.

C08-002A/B and C08-003A/B (see MS[1] pages 85-86, 91-95, 111-112)

In study C08-002A/B (aHUS patients who were plasma therapy resistant) and study C08-003A/B (aHUS patients who were plasma therapy sensitive), improvements were generally observed for all measured endpoints (primary efficacy, TMA, renal function and quality of life) from baseline to 26 weeks follow-up (Table 8). However, these improvements appeared to be more pronounced in patients who were resistant to plasma therapy. With longer-term eculizumab therapy, all endpoints were generally maintained or improved in both studies (week 64 in study C08-002A/B or week 62 in study C08-003A/B); however, by week 114 a plateau type effect was observed for most outcomes, particularly in study C08-002A/B. It is noteworthy that in study C08-002, dialysis was discontinued in four out of five patients (80%) who had required dialysis at the time of initiation of eculizumab, and these patients remained dialysis-free throughout eculizumab treatment.

Although the MS[1] did not provide any detailed results by subgroup (including rationale and *a priori* analysis plan for subgroups), it does state that in studies C08-002A/B and C08-003A/B, no significant differences in haematological normalisation, 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 (see MS[1] page 85).

Table 8: Summary of results for study C08-002A/B and C08-003A/B (ITT analysis except where noted)

Study	Efficacy variables				Thrombotic microangiography			
	Change in platelet count (x 10^9/L) from baseline[a], mean (95%CI)	Normalisation of platelet count, n (%)	TMA event-free status[b], n (%)	Haematologic normalisation,[c] n (%)	TMA intervention rate		Complete TMA response,[d] n (%)	Change in Hb > 20g/L, n (%)[e]
					Pre-eculizumab rate, median (min; max).	Post-eculizumab rate, median (min; max)		
C08-002A/B (n=17)								
26 weeks	73 (40 to 105); p=0.0001	14/17 (82%)	15/17 (88%)	13/17 (76%)	0.88 (0.04; 1.59)	0 (0; 0.31); p<0.0001	11/17 (65%)	11/17 (65%)
64 weeks[f]	91[g] (67 to 116); p<0.0001	15/17 (88%)	15/17 (88%)	15/17 (88%)	-	0 (0; 0.31); p<0.0001	13/17 (76%)	13/17 (76%)
114 weeks[f]	88 (63 to 112); p <0.0001	15/17 (88%)	15/17 (88%)	15/17 (88%)	-	0 (0; 0.31); p<0.0001	13/17 (76%)	13/17 (76%)
C08-003A/B (n=20)								
26 weeks	5 (-17 to 28); p=NS[h]	18/20 (90%)	16/20 (80%)	18/20 (90%)	0.23 (0.05; 1.09)	0 (0; 0); p<0.0001	5/20 (25%)	9/20 (45%)
62 weeks[f]	NR	19/20 (95%)	17/20 (85%)	18/20 (90%)	-	0 (0; 0); p<0.0001	7/20 (35%)	10/20 (50%)
114 weeks[f]	NR	18/20 (90%)	19/20 (95%)	18/20 (90%)	-	0 (0; 0); p<0.0001	11/20 (55%)	13/20 (65%)

Hb, haemoglobin; ITT, intention-to-treat; MID, minimally improved difference (i.e. achievement of clinically meaningful threshold of 0.06); NR, not reported; TMA, thrombotic microangiography

[a] *Primary endpoint in study C08-002A/B*

[b] *Primary endpoint in study C08-003A/B defined as no decrease in platelet count of > 25% AND no plasma exchange/ plasma infusion AND no new dialysis for ≥12 consecutive weeks*

[c] *Hematologic Normalization is defined as the normalization of platelet counts and lactate dehydrogenase levels sustained for ≥ 2 measurements over ≥ 4 weeks*

[d] *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).*

[e] *Sustained effect defined as ≥ 2 measurements over ≥ 4 weeks*

[f] *Median duration except where noted*

[g] *Data at 60 weeks*

[h] *Data from Legendre et al*[39]

Table 8 (cont.): Summary of results for study C08-002A/B and C08-003A/B (ITT analysis except where noted)

Study	Renal function				Quality of life	
	CKD improvement by ≥1 stage,[e] n (%)	eGFR change from baseline (mL/min/1.73 m^2), mean (95% CI)	eGFR improvement ≥15 mL/min/1.73 m^2 [e], n (%)	Decrease in proteinuria by ≥ 1 grade [i]	HRQoL change (mean point) from baseline (95% CI)	HRQoL, evaluable patients achieving MID of 0.06[e]
C08-002A/B (n=17)						
26 weeks	10/17 (59%)	31 (17 to 45); p<0.0001	8/17 (47%)	12/15 (80%)	0.32 (0.27 to 0.38);p<0.0001[m]	12/15 (80%)
64 weeks[f]	11/17 (65%)	31 (15 to 46); p<0.0001	9/17 (53%)	9/11 (82%)[j]	0.32 (0.27 to 0.38);p<0.0001[m]	13/15 (87%)
114 weeks[f]	12/17 (71%)	32[k] (15 to 49); p<0.0008	10/17 (59%)	7/9 (78%)[k]	0.33 (0.30 to 0.36);p=0.001	13/15 (87%)
C08-003A/B(n=20)						
26 weeks	7/20 (35%)	6.1 (3.3 to 8.8);p<0.0001	1/20 (5%)	8/16 (50%)[n]	0.12 (0.07 to 0.17);p<0.0001[m]	12/15 (80%)[o]
62 weeks[f]	9/20 (45%)[h]	8.3 (4.8 to 11.7);p<0.0001	3/20 (15%)	7/9 (78%)[j]	0.13 (0.08 to 0.18);p<0.0001	13/15 (87%)[o]
114 weeks[f]	12/20 (60%)	7.1[k] (-0.30 to 14); p<0.05[l]	8/20 (40%)	NR	0.14[k] (0.10 to 0.18;p<0.0001	13/15 (87%)[o]

Hb, haemoglobin; ITT, intention-to-treat; MID, minimally improved difference (i.e. achievement of clinically meaningful threshold of 0.06); NR, not reported; TMA, thrombotic microangiography
[a] *Primary endpoint in study C08-002A/B*
[b] *Primary endpoint in study C08-003A/B defined as no decrease in platelet count of > 25% AND no plasma exchange/ plasma infusion AND no new dialysis for ≥12 consecutive weeks*
[c] *Hematologic Normalization is defined as the normalization of platelet counts and lactate dehydrogenase levels sustained for ≥ 2 measurements over ≥ 4 weeks*
[d] *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).*
[e] *Sustained effect defined as ≥ 2 measurements over ≥ 4 weeks*
[f] *Median duration except where noted*
[g] *Data at 60 weeks*
[h] *Discrepancy in data (MS[1] suggest 4/20 which appears to be a typographical error), thus data from Legendre et al.[39]*
[i] *Evaluable patients*
[j] *Data at 52 weeks*
[k] *Data at 96 weeks*
[l] *Data reported as significant; however, the confidence intervals suggest not significant*
[m] *Discrepancy in data between Table C11, C12 (p92-95) and Table D12, D13 (p162, 164) in the MS[1] (Data in Table D12 and D13 correspond to the data in the original publication by Legendre et al.[39] e.g. C08-002, 26 weeks: 0.32 (0.24 to 0.39);p<0.001; 64 weeks; 0.30 (0.25 to 0.35);p<0.001; C08-003, 26 weeks: 0.10 (0.05 to 0.15);p<0.001)*
[n] *Discrepancy in data: Legendre et al[39] suggest 6/11 (55%)*
[o] *Discrepancy in data: Legendre et al.[39] suggest the following: C08-003, 26 weeks: 8/11 (73%); 62 weeks, 8/11 (73%); 114 weeks, not available*

C10-003 and C10-004 (see MS[1] pages 85-86, 96-102, 112-114)

Unpublished interim results from study C10-003 (paediatric patients with aHUS) and C10-004 (adult patients with aHUS) showed [redacted]. It is noteworthy that in study C10-003, nine of the 11 patients (82%) who were on dialysis at baseline no longer required dialysis during eculizumab treatment, [redacted].

The MS[1] did not provide any detailed results by subgroup (including rationale and *a priori* analysis plan for subgroups); however, it does state (page 113) [redacted]. Similarly, the MS[1] states (page 114) [redacted]

Table 9: Summary of results for study C10-003 and C10-004 (Interim ITT analyses except where noted)

Study	Efficacy variables		Thrombotic microangiography					
	Normalisation of platelet count,[a] n (%)	[redacted]	Complete TMA response,[c] n (%)	Complete TMA response[d] with preservation of renal function	[redacted]	Complete hematologic response[f]	[redacted]	[redacted]
C10-003 (n= 22[g])								
26 weeks	21/22 (96%)	[redacted]	14/22 (64%)	NR	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C10-004 (n=41[g])								
26 weeks	40/41 (98%)	[redacted]	NR	30/41 (73%)	[redacted]	36/41 (88%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]*; eGFR, estimated glomerular filtration rate;* [redacted]*; ITT, intention-to-treat;* [redacted]*; NR, not reported; TMA, thrombotic microangiography*

[redacted]

Table 9 (cont.): Summary of results for study C10-003 and C10-004 (Interim ITT analyses except where noted)

Study	Renal function					Other
	[redacted]	[redacted]	**eGFR improvement ≥15 mL/min/1.73 m^2 [a], n (%)**	[redacted]	[redacted]	[redacted]
C10-003 (n= 22[a])						
26 weeks	[redacted]	[redacted]	19/22 (86%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C10-004 (n=41[a])						
26 weeks	[redacted]	[redacted]	22/41 (54%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]*; eGFR, estimated glomerular filtration rate;* [redacted]*; ITT, intention-to-treat;* [redacted]*; NR, not reported; TMA, thrombotic microangiography*

[redacted]

C09-001r (see MS[1] pages 85, 95-96, 112)

In the retrospective C09-001r study (paediatric and adult patients with aHUS), improvements were observed for all measured endpoints, particularly platelet count normalisation and TMA event-free status from baseline to 26 weeks (Table 10). Despite the lack of details on the subgroup analyses undertaken, the MS[1] stated (page 112) that 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 out of eight (50%) paediatric patients who previously required dialysis were able to discontinue dialysis once on eculizumab treatment.

Table 10: Summary of results for the C09-001r retrospective study

Study	Efficacy variables		Thrombotic microangiography				Renal function
	Normalisation of platelet count, n (%)	TMA event-free status[a], n (%)	TMA intervention rate		Complete TMA response,[b] n (%)	Change in Hb > 20g/L, n (%)[e]	eGFR improvement ≥15 mL/min/1.73 m^2 [a], n (%)
			Pre-eculizumab rate, median (min; max).	Post-eculizumab rate, median (min; max)			
C09-001r (n=30)							
26 weeks	25/30 (83%)	20/30 (67%)	0.34 (0.00; 2.38)	0 (0; 0.41); p<0.0001	10/30 (33%)	13/30 (43%)	11/30 (37%)

eGFR, estimated glomerular filtration rate; Hb, haemoglobin; TMA, thrombotic microangiography
[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] *Complete TMA response defined as hematologic normalization and improvement in renal function defined as ≥ 25% decrease in serum creatinine from baseline.*

4.2.4.2 Safety and tolerability (as reported in MS[1]: p86-87, 102-109)

This section presents the main safety evidence from all participants who received at least one dose of study drug.

Discontinuation of eculizumab

In the two prospective studies, five patients discontinued eculizumab therapy (C08-002A/B, n=4 and C08-003A/B, n=1) following completion of the 26-week treatment period. The reasons for discontinuation included the following: one due to meeting an exclusion criterion (Systemic Lupus Erythematosus [SLE] diagnosis), one due to an AE unrelated to eculizumab treatment (pancytopenia), and three patients chose not to continue treatment in the extension phase (one patient discontinued due to personal reasons but restarted eculizumab outside of the study due to declining clinical condition, one patient was lost to follow up and one patient became dialysis-free during the study and had no loss of kidney function as of last follow-up 8 weeks post discontinuation [see response to clarification questions[34] #2]). During the extension study period, two patients discontinued eculizumab treatment in study C08-002A/B (due to worsening and decreased renal function that were deemed unrelated to study treatment) and one patient in study C08-003A/B (due to gastrointestinal haemorrhage leading to death that was deemed unrelated to study drug).

An interim analysis of the C10-003 prospective study (paediatric aHUS patients) reported three discontinuations before completion of the 26-week treatment period. [redacted]

Three adult patients were withdrawn from the C10-004 study prior to the completion of the 26-week treatment period. [redacted] In retrospective study C9-001r, 13 patients discontinued eculizumab therapy. Reasons for discontinuation included (as reported in the EMA assessment report of eculizumab[41] and the manufacturer's response to clarification questions[34] #2) severe TMA complications (n=6), death (n=2, unrelated to study drug) and chronic

dialysis before and after eculizumab (n=2). In the remaining three patients, there was no evidence of TMA complications and no reasons for discontinuation were provided in the manufacturer's clarification response.

4.2.4.3 Adverse events

The adverse events (AE) data in the MS[1] (pages 102-107) were limited to treatment-related AEs for all prospective published (C08-002A/B and C08-003A/B) and unpublished (C10-003 and C10-004) studies and a retrospective study (C09-001r). Additional data (including details of all AEs) were provided in several separate documents.[51-54]

Although nearly all patients reported one AE in study C08-002A/B (n=17; median duration of eculizumab treatment, 38 weeks) and C08-003A/B (n=20; median duration of eculizumab treatment, 40 weeks), only 43% (16/37) of patients had an AE that was considered by the study investigators to be study drug-related (reported as definite, probable or possible). Treatment-related AEs occurred in 59% (n=10) of patients (who were plasma therapy resistant) in study C08-002A/B and 30% (n=6) of patients (who were plasma therapy sensitive) in study C08-003A/B. Serious adverse events (SAEs) were reported more frequently in study C08-002A/B (n=15, 88%) than in study C08-003A/B (n=5, 25%). However, only five patients were considered to have had a treatment-related SAE (C08-002A/B: n=3; C08-003A/B: n=2). Leucopoenia, nausea, vomiting and accelerated hypertension were the most common treatment-related AEs in study C08-002A/B, whereas headache, leucopoenia and lymphopenia were the most common treatment-related AEs in study C08-003A/B. A summary of the most common treatment-related AEs in study C08-002A/B and C08-003A/B as reported by the manufacturer, including supplemental information, has been constructed and re-tabulated in a consistent and more transparent format by the ERG (see Table 11).

Additional data from the extension study period (C08-002A/B: median duration of eculizumab treatment, 100 weeks; C08-003A/B: median duration of eculizumab treatment, 114 weeks)[52] provided a similar AE profile for treatment related AEs (see Table 12). [redacted]

Table 11: Treatment related AEs[a] reported by ≥5% of patients in study C08-002A/B (median treatment duration 38 weeks) and C08-003A/B (median treatment duration of 40 weeks) (see p103-105, MS[1] and p21-23, Alexion Pharmaceuticals Inc[52])

	C08-002A/B (n=17)		C08-003A/B (n=20)		Total (n=37)	
Adverse event	**All**	**Severe**	**All**	**Severe**	**All**	**Severe**
Patients with at least 1 drug related AE	10 (59%)	1 (6%)	6 (30%)	2 (10%)	16 (43%)	3 (8%)
Patients without drug related AEs	7 (41%)	NR	14 (70%)	NR	21 (57%)	NR
Blood and Lymphatic System Disorders	2 (12%)	0	3 (15%)	0	5 (14%)	0
Abnormal clotting factor	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Anaemia	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Leukopenia	2 (12%)	0	2 (10%)	0	4 (11%)	0
Lymphopenia	0	NR[b]	2 (10%)	0	2 (5%)	0
Ear and Labyrinth Disorders	1 (6%)	NR[b]	1 (5%)	0	2 (5%)	0
Vertigo	1 (6%)	NR[b]	1 (5%)	0	2 (5%)	0
Gastrointestinal Disorders	2 (12%)	0	1 (5%)	1 (5%)	3 (8%)	1 (3%)
Diarrhoea	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Nausea	2 (12%)	0	0	NR[b]	2 (5%)	0
Vomiting	2 (12%)	0	0	NR[b]	2 (5%)	0
Peritonitis	0	0	1 (5%)	1 (5%)	1 (3%)	1 (3%)
General Disorders and Administration Site Conditions	2 (12%)	0	1 (5%)	0	3 (8%)	0
Asthenia	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Pyrexia	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Extravasation	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Infection and Infestations	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
BK virus infection	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Infections and Infestations	3 (18%)	0	1 (5%)	0	4 (11%)	0
Herpes zoster	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Impetigo	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Influenza	NR[b]	0	NR[b]	0	NR	0
Urinary tract infection	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Investigations	2 (12%)	0	0	NR[b]	2 (5%)	0
Haematocrit decreased	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Haemoglobin decreased	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Nervous System Disorders	2 (12%)	0	2 (10%)	0	4 (11%)	0
Headache	1 (6%)	0	2 (10%)	0	3 (8%)	0
Tremor	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Respiratory, Thoracic and Mediastinal Disorders	0	NR[b]	1 (5%)	0	1 (3%)	0
Cough	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Rhinorrhoea	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Skin and Subcutaneous Tissue Disorder	2 (12%)	0	1 (5%)	0	3 (8%)	0
Dermatitis	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Erythema	1 (6%)	0	NR[b]	NR[b]	1 (3%)	0
Alopecia	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0

	C08-002A/B (n=17)		C08-003A/B (n=20)		Total (n=37)	
Pruritus	NR[b]	NR[b]	1 (5%)	0	1 (3%)	0
Vascular Disorders	3 (18%)	1 (6%)	1 (5%)	1 (5%)	4 (11%)	2 (5%)
Accelerated Hypertension	2 (12%)	0	0	NR[b]	2 (5%)	0
Hypertension	1 (6%)	1 (6%)	0	0	1 (3%)	1 (3%)
Vein disorder	NR[b]	0	1 (5%)	1 (5%)	1 (3%)	1 (3%)

AE, adverse event; NR, not reported
[a] AEs classified according to MedDRA Version 11.0 dictionary and contributed to the summary table if they occurred on the same day as the first eculizumab dose or after
[b] Assumed zero AEs by the ERG

Table 12: Update of treatment related AEs[a] reported by ≥5% of patients in study C08-002A/B (median treatment duration 100 weeks) and C08-003A/B (median treatment duration of 114 weeks) (see p21-23, Alexion Pharmaceuticals Inc[52])

	C08-002A/B (n=17)		C08-003A/B (n=20)		Total (n=37)	
Adverse event	**All**	**Severe**	**All**	**Severe**	**All**	**Severe**
Patients with at least 1 drug related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and Labyrinth Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and Subcutaneous Tissue Disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Accelerated Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vein disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; NR, not reported
[a] AEs classified according to MedDRA Version 11.0 dictionary and contributed to the summary table if they occurred on the same day as the first eculizumab dose or after
[b] Assumed zero AEs by the eRG

In study C10-003 (eculizumab in paediatric aHUS patients), [redacted]

[redacted]

In study C10-004 (eculizumab in adult aHUS patients) [redacted]

In the retrospective C09-001r study, 22 (73%) of the 30 patients reported at least one AE. Pyrexia (30%) and diarrhoea (27%) were the most frequently recorded AEs in the retrospective study (see Table 13). Upper respiratory tract infections were also common with 20% (6/30) patients reporting this AE whilst receiving eculizumab.

Clinical advisors to the ERG suggest that there is uncertainty with respect to whether these events are a result of damage caused prior to starting eculizumab treatment or whether eculizumab has not fully eliminated extra-renal manifestations of the disease.

Table 13: Summary of AEs reported by ≥10% of patients in study C09-001r (see MS[1] pages 105-106)

Adverse Events	Total (n=30)
Patients with at least 1 AE	22 (73%)
Patients with no AE	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%)
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%)
AE, adverse event	

4.2.4.4 Deaths

No deaths were reported in study C08-002A/B, C08-003A/B, [redacted] during the 26-week study. However, at the 3-year data update (extension period) in the C08-002A/B and C08-003A/B study, one death (due to gastrointestinal haemorrhage) was noted in study C08-003A/B and was determined not to be related to eculizumab (see response to clarification questions[34] #10). In the retrospective C09-001r study, there were two (7%) deaths that were related to cerebrovascular accident (stroke) and fatal carotid artery dissection; these were determined by the study investigators to be unrelated to eculizumab.

4.2.4.5 All cases of meningococcal infection

There were no reported meningococcal infections with eculizumab treatment of aHUS patients in the prospective studies (C08-002A/B) or C08-003A/B). However, there was a single meningococcal infection reported in an aHUS patient recruited into study C09-001r, which occurred after the data

cut-off and was captured as a post-marketing report. This patient fully recovered without sequelae and remained on eculizumab. In the ongoing C10-004 study, two meningococcal infections have been reported (see MS[1] page 107). Both infections resolved with appropriate treatment, although one led to permanent discontinuation of eculizumab treatment and withdrawal from the study.

4.3 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees. This ERG report does not include a detailed discussion of non-scientific opinion submitted by other consultees or expert testimony provided by other consultees to the appraisal process; however, some of this information has been used to inform the discussion sections of this report. The following submissions were made to NICE:

- Royal College of Physicians (RCP)
- Kidney Research UK
- aHUS UK
- aHUS Action

4.4 Additional work on clinical effectiveness undertaken by the ERG

In light of the problems with the limited process used to identify and report evidence for the specified comparators within the MS, the ERG examined the registry studies mentioned in the submission in order to make the outcomes of these studies more transparent. This does not represent a systematic review, and the ERG cannot guarantee that other relevant evidence for standard care does not exist.

4.4.1 Detailed reporting of registry study outcomes

Five registry sources for aHUS patients on standard care are mentioned in the MS.[31,33;8,11,32] As the manufacturer has not presented adequate information from these sources the ERG has briefly summarised the studies and their outcomes as they are important for understanding the prognosis of aHUS on patients receiving standard care. One study[8] has been excluded as it is based on patients from the same registry as Noris *et al*,[11] with the latter publication being more recent.

Table 14 presents an overview of the registry studies. Patients were only explicitly diagnosed with aHUS in two of the studies,[11,32] the other two studies especially the detectable ADAMTS13 or ADAMTS13 ≥10% subgroups may contain aHUS patients but unlike the other two studies may contain non-aHUS patients as well. For this reason, this discussion focusses on Fremeaux-Bacchi *et al*[32] and Noris *et al*.[11] The Fremeaux-Bacchi *et al* study reports information on 214 patients diagnosed and treated in France between 2000 and 2008. Patient outcomes were reported for a paediatric and adult population and by genetic mutation at 1- and 5-years. The study does not state how patients were recruited but does state it was a nationwide study to identify patients with aHUS. The Noris *et al* study reports on 273 patients recruited consecutively to the International Registry of Recurrent and Familial HUS/TTP between 1996 and 2007. The majority of patients in the study were from Italy or elsewhere in Europe, with the remaining patients having been recruited from around the world. Patient outcomes are reported for all patients (paediatric and adult populations combined) and by genetic mutation. The proportion of patients in remission, complete remission (defined as normalisation of hematologic parameters and renal function), partial remission (defined as normalisation of hematologic parameters with renal sequelae), ESRD, and death were reported after the initial aHUS episode and at 3 years. Plasma therapy and transplant outcomes at 1-year were also reported.

Table 14: Characteristics of aHUS/TMA registry studies discussed in the MS

Registry	Patient population	Number of patients	Age	Methods of recruitment	Country	Duration of follow-up	Treatments	Genetic mutation	Outcomes reported
Coppo *et al* (2010)[31]	Patients experiencing TMA	241 54 detectable ADAMTS13 activity	Adults (>18 years)	Consecutively and nonselectively from 17 French centres and their affiliated regional centres 2000 -2007	France	Mean follow-up 17.8 months	Plasma infusion, steroids, rituximab, vincristine, splenectomy	Not reported	Time to platelet count recovery, survival, flare-up episode(s), relapse, ESRD
Hovinga *et al* (2010)[33]	TTP registry – patients for whom plasma exchange was requested	261 - (patients who had ADAMTS13 activity measured at initial diagnosis) 201 - ADAMTS13 ≥10%	Paediatric and adult population	Consecutive patients for whom plasma exchange was requested 1989 - 2008	US - Oklahoma	Median follow-up 4.6 years	Plasma exchange	Not reported	Survival and relapse
Fremeaux-Bacchi *et al* (2013)[32]	aHUS diagnosed patients– excluded secondary aHUS (except in pregnancy)	214 89 children 125 adults	Paediatric and adult population	2000-2008 – patients who met the diagnostic criteria for aHUS	France	Up to 20 years – outcomes reported at 1 month, 1 year and 5 years	High and low frequency plasma exchange	Yes – genetic mutations reported	ESRD, survival, relapse
Noris *et al* (2010)[11]	aHUS diagnosed patients	273	Paediatric and adult population	Consecutive patients registered within the International Registry of Recurrent and Familial HUS/TTP 1996 – 2007	58% Italy, 15% other European countries, 14% North America, 2% South America, 2% Africa, 1% Asia, 8% Middle East	Up to 10 years – outcomes reported after initial episode and 3 years	Plasma exchange, transplantation	Yes – genetic mutations reported	Remission (partial and complete), ESRF, death, response to plasma, outcome of transplantation

Table 15 summarises the reported clinical outcomes from the four registry studies mentioned in the MS.[1] The presented results for Fremeaux-Bacchi *et al* and Noris *et al* are for aHUS patients. Results for Hovinga *et al* and Coppo *et al* are presented for the ADAMTS13 ≥10% and detectable ADAMTS13 subgroups respectively. There are likely to be differences in prognosis and outcomes between aHUS-specific patients and other populations. The discussion therefore focuses on results from Fremeaux-Bacchi *et al*[32] and Noris *et al*[11] as these reported outcomes pertain to patients who have been explicitly diagnosed with aHUS.

Outcomes are reported at different timepoints therefore comparison between the registries at individual time points is not possible. Survival is higher in the aHUS registries than in the other two registries. The survival rate found in Hovinga *et al* at a median follow-up of 4.6 years is substantially lower than that in Fremeaux-Bacchi *et al* at 5 years and the survival rate found in Coppo *et al* at 18 months is lower than Fremeaux-Bacchi *et al* at 5 years and Noris *et al* at 3 years. The substantially lower survival rate reported by Hovinga *et al* may be due to the inclusion of patients recruited from as far back as 1989 and due to the characteristics of the recruited patient cohort. For the aHUS-specific registries, Fremeaux-Bacchi *et al* reports more favourable survival estimates than Noris *et al*. This may be due to the start date of recruiting patients and because Noris *et al* included patients recruited worldwide and standards of diagnosis and care may vary geographically. The earliest recruited patients in the Noris *et al* study were from 1996 and the earliest from Fremeaux-Bacchi *et al* were from 2000. The understanding of the disease has improved substantially over the past 10 to 15 years and therefore the lower survival seen in the Noris *et al* study may reflect this. In the Fremeaux-Bacchi *et al* study survival was notably higher in the adult population than in the paediatric population.

Similar rates of ESRD were found in both Noris *et al* and Fremeaux-Bacchi *et al*. Noris *et al* reported 45% of patients in ESRD at 3 years; the Fremeaux-Bacchi *et al* study found 41% of patients in ESRD at 1 year and 49% at 5 years (paediatric and adult populations combined). It is evident from the Fremeaux-Bacchi *et al* study that the proportion of patients reaching ESRD was higher in the adult population than in the paediatric population.

The comparison of other reported outcomes between studies is more difficult as Fremeaux-Bacchi *et al* report relapse rates whereas Noris *et al* report rates of remission and the proportion of successful transplants. The proportion of relapses in Fremeaux-Bacchi *et al* relate to the number of patients who did not die or reach ESRD during their first aHUS episode. Of these patients, 25% of paediatric patients and 29% of adult patients suffered their first relapse during the first year. After the first year 18% of paediatric patients and 5% of adult patients suffered their first relapse. Forty-three percent of paediatric patients relapsed during follow-up and 35% of adult patients relapsed during follow-up.

Noris *et al* report the proportions of patients in remission at the first episode and at 3 years, 60% and 46% respectively, which are slighter lower than would be expected given the relapse rate reported by Fremeaux-Bacchi *et al*. Of those patients who underwent transplant 33% of the paediatric patients and 45% of the adult patients had a good kidney transplantation outcome at 1-year.

Whilst this is not a full systematic review, this information has been extracted and tabulated in an open and transparent manner. These estimates of the prognosis of aHUS patients receiving standard care appear considerably less pessimistic than the general statements throughout within the MS[1] regarding the outlook for aHUS patients without eculizumab.

Table 15: Key outcomes reported within registry studies

Registry	Population	Time outcome reported	Survival		ESRD		Relapse		Remission	Successful transplant	
			Children	Adults	Children	Adults	Children	Adults		Children	Adults
Coppo *et al* (2010)	Detectable ADAMTS13 activity	Mean follow-up 17.8 months	-	87%	-	21%	-	14%	-	-	-
Hovinga *et al* (2010)	ADAMTS13 ≥10%	Median follow-up 4.6 years	68%		Not reported		4%		-	-	-
Fremeaux-Bacchi *et al* (2013)	aHUS	1 month	87/89 (98%)	125 (100%)	13 (15%)	57 (46%)	-	-	-	-	-
		1 year	83/89 (93%)	124/125 (99.2%)	20 (23%)	69 (55%)	25% (16/65)* †	29% (19/65)*†	-	-	-
		5 years	83/89 (93%)	124/125 (99.2%)	26 (29%)	79 (63%)	18% (12/65) ‡	5% (3/65) ‡	-	-	-
		Last follow-up	82/89 (92%) 14 years	123/125 (98.4%) 7 years	28 (32%)	87 (70%)	-	-	-	-	-
Noris *et al* (2010)	aHUS	Outcome of initial episode	92%		36%		-	-	60%	-	-
		1 year (post-transplant)	-		-		-	-	-	33% (8)	45% (18)
		3 years	89%		45%		-	-	46%		

**1st relapse ≤1 year, † patients who had not died or reached ESRD, ‡ 1st relapse > 1 year,*

4.4.2 Case reports and case series

The MS[1] lists 60 case reports on the use of eculizumab to treat aHUS and two case series, all of which were excluded from the manufacturer's systematic review. The manufacturer's response to the clarification questions (#17) notes that *"…case series were not considered relevant to the scope of the submission due to their wide variability of dose protocol and treatment duration that is inconsistent with the SmPC and the proposed use of eculizumab for aHUS in England."*[34] The ERG note that despite the inherent biases associated with this study type, the inclusion of such evidence in the systematic review may have increased the evidence base and strengthened the credibility of the review.[35] For completeness, this section provides a brief summary of the evidence from the two case series reports reported by Zuber *et al.*[55,56] However, the ERG was unable to review and summarise all the individual case reports within the timelines of this appraisal.

Zuber *et al.*[56] report a series of 28 case reports including 24 patients, 11 of whom were children and all of whom were given eculizumab as curative therapy. Ten of these patients had transplanted kidneys and 14 had native kidneys. Complement mutations were found in 15 (62.5%) patients. Seven of the case reports in Zuber *et al*[56] are not included in Table C4 (pages 67-69) of the MS.[57-63] It is not clear how the authors selected the case reports for inclusion in this report. Key results for the 24 patients in Zuber *at al*[56] are summarised in Table 16.

Table 16: Response to eculizumab in Zuber *et al*[56] (case series)

Response to eculizumab	**Children (n=11)**	**Adults (n=13)**
Normalisation of aHUS-related haematological features	11/11 (100%)	13/13 (100%)
Full recovery of baseline renal function	8/10 (80%)	4/13 (30.7%)
Decrease in creatinine level greater than 25%	9/10 (90%)	9/13 (69.2%)
Percentage reduction in creatinine level	63.3 ± 28.8	41.9 ± 29.5
Median follow-up	22 months (range 2.5-42 months)	15 months (range 2-49 months)
Mean ± SD creatinine level at last follow-up	53.9 ± 34.5 µmol/l	16.2 ± 96.2 µmol/l

In another study, Zuber *et al*[55] describes 22 renal transplant patients who received off-label therapy with eculizumab, 13 of whom were not reported in Table C4 (pages 67-69) of the MS. Four of these were published[57,58,61,62] and the remaining reports were unpublished personal communications from V Gueutin (n=1), M Hourmant (n=1), A. Lahoche (n=1) E. Rondeau (n=1) S Krid (n=1) and J Zuber (n=4). Zuber *et al*[55] chose the patients for the case series by contacting French renal transplant centres, contacting authors of congress abstracts and use of eculizumab in peer reviewed journals. Both children and adults were included in the case series. Nine patients were given prophylactic

aHUS to prevent post-transplant aHUS recurrence. Of these 9 patients, 8 experienced a successful recurrence-free post-transplant course after a median follow-up of 14.5 months (range 2-39). Thirteen patients were treated with eculizumab for post-transplant a HUS recurrence. A complete reversal of aHUS activity was obtained in all of them. The delay of eculizumab after the onset of the aHUS episode was found to be inversely correlated with the degree of renal function improvement. Three patients in whom eculizumab was stopped all experienced a relapse.

4.5 Conclusions of the clinical effectiveness section

4.5.1 Completeness of the MS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the MS[1] is largely based on a systematic review of eculizumab for the treatment of patients with aHUS. The ERG is confident that all relevant studies (published and unpublished) of eculizumab were included in the MS, including data from ongoing extension studies. However, it is not entirely clear if all relevant comparator studies were identified as no proper attempt was made to search for these and there is no transparent evidence in the MS that a systematic review of standard care was undertaken. The reporting of outcomes from registry studies in the MS is neither comprehensive nor transparent. Additional evidence in the form of case series (and case studies) was also identified; however, these studies were excluded from the manufacturer's review. Despite the inherent biases associated with this study type, the inclusion of such evidence in the systematic review may have increased the evidence base and strengthened the credibility of the manufacturers review.[35]

4.5.2 Interpretation of treatment effects reported in the MS in relation to relevant population, interventions, comparator and outcomes

A key issue that may limit the robustness of the efficacy and safety data reported in the MS relates to the study design of the included studies. Due to the to the absence of a control group in all four Phase 2, open label, non–randomised, single arm prospective studies (C08-002A/B, C08-003A/B, C10-003 and C10-004), inference of treatment effects (including magnitude) may be confounded, and it remains uncertain whether all patients would respond to treatment with eculizumab or would even require treatment, as reports indicate that some patients with aHUS experience natural recovery without any therapy.[12,64] Patient registries would provide useful insights into the natural history of aHUS and would provide a greater understanding of the relative clinical effectiveness of eculizumab compared to patients receiving other therapies.

The ERG appreciates that treatment-related AEs, as reported in the MS, are important but all reported adverse events are required, as a high proportion of patients suffering mild effects could still represent a reasonably high cumulative QALY loss. Additional data (including details of all AEs) were

provided in separate documents; however, none of these were tabulated or reported in the MS. More importantly, AEs deemed to be treatment-related were identified by the study investigators (no details were available on whether safety outcomes were also assessed by an independent endpoint assessment adjudication committee) and as such may have been open to bias. It is not clear how this may have influenced or biased the results.

4.5.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties in the clinical evidence primarily relate to optimal dosing and duration of treatment. Further details are provided below.

Optimal dosing

Although EMA approved dosing recommendations for aHUS patients are used in the prospective studies, there are no details or justification in the MS regarding the selected dosing regimens for patients with aHUS. After seeking further clarification (see response to question #7) from the manufacturer (limited information provided) and information provided in the EMA assessment report,[41] it appears that an optimal dosing strategy for aHUS patients was based on dosing simulations of pharmacokinetic and pharmacodynamics data for eculizumab from two prospective studies (C08-002A/B and C08-003A/B) and a retrospective study (C09-001r). Based on the results of these simulations, the weight-based doses and dose schedules were developed for aHUS. The EMA assessment report (page 12) states that *"…a dose-response study might have helped in the selection of the optimal dose. Unfortunately this has not been done and no other doses have been tested in the studies conducted. Therefore, the question is whether the proposed dosing regimens can be accepted on the basis of their benefit/risk balance. The relatively high dose proposed in this indication may not be optimal particularly for long-term side effects that could be avoided with reduce posology. The applicant agreed to discuss the feasibility of a further study investigating efficacy and safety of lower doses at post approval."*

Despite this, the ERG is not aware of any published (or planned) dose-response studies that have been undertaken to establish an optimal dose. The manufacturer states that there is no evidence to support flexible dosing in any patient setting (see response to clarification questions[34] #7); however, the ERG is aware of a single case report (a 50 year old woman with aHUS) which suggests that a lower eculizumab maintenance dose of 600 mg every two weeks, rather than the recommended 1200 mg every two weeks, is effective in improving renal function. Similarly, a patient organisation (aHUS UK) submission to NICE[65]states that *"Although the manufacturers maintain that the drug has to be taken as prescribed in the prescribed dose for life, CPAG recommended recently that NHS investigate whether flexibility in dosing might be possible. We have evidence that in at least one European*

country, Italy, where the drug has been freely available for years, that flexible dosing, based on strict clinical criteria and patient monitoring, is working successfully." The ERG has not seen (or been provided with) this evidence and cannot verify its reliability.

Duration of treatment

The optimal duration of treatment with eculizumab is unclear. The SmPC[24] recommends long-term (lifelong) treatment of aHUS unless discontinuation is clinically indicated. However, there is no long-term safety and efficacy data from prospective studies to support this. The SmPC[24] and the manufacturers' response to clarification questions[34] (questions #7 and #11) notes that discontinuation of eculizumab therapy may be associated with increased risk of relapse. Similarly, published case reports have shown that a reduced dose or discontinuation of eculizumab treatment may lead to rapid deterioration in organ function.[63,66-68] Nevertheless, the current interim national service for aHUS in Newcastle, implemented by NHS England, considers withdrawing (or restarting) eculizumab therapy based on a set of criteria that depend on the patients circumstances (Table 17). The ERG notes that these criteria appear to be based on consensus. Nevertheless, aHUS Action[69] and other investigators[70,71] call for well controlled prospective studies (ideally RCTs) to address the issue of treatment duration and whether all patients need to continue long-term therapy.

Table 17: Interim national aHUS service criteria for withdrawing (or restarting) eculizumab therapy[69]

Consideration	Criteria for eculizumab withdrawal
Eculizumab therapy ***would be*** withdrawn in the following circumstances?	a) A newly diagnosed patient who does not have any complement abnormality (genetic or autoantibody) who despite at least four months of treatment does not show any recovery of renal function and remains on dialysis. In these patients, measurement of platelet count, lactate dehydrogenase, haptoglobins and haemoglobin are undertaken every two weeks to determine whether there is any recurrence of an extra-renal TMA which may lead to a reintroduction of eculizumab. b) A newly diagnosed patient who on screening is found to have only a mutation in MCP (CD46) and has completely recovered renal function with no evidence of an ongoing TMA. Studies undertaken before the use of eculizumab show that the natural history of the disease in such patients is often good with spontaneous complete recovery of renal function. If patients developed frequent relapses then use of long-term prophylactic eculizumab would be appropriate. c) A newly diagnosed patient who on screening is found to have only factor H autoantibodies. The prognosis in this group of patients is good with many patients not relapsing.
Eculizumab therapy ***would not b***e withdrawn in the following circumstances:	a) In a patient who had received eculizumab to prevent recurrent disease post-transplant where there was a history of a previous transplant being lost to recurrent disease. b) In a patient known to have a mutation which is associated with a high rate of recurrence and a poor prognosis (for instance the CFH/CFHR1 hybrid). c. In all other patients' withdrawal of eculizumab therapy would only be considered in the context of a RCT.
CFH, complement factor H; CFHR1, complement factor H-related proteins; MCP (CD46), Membrane Cofactor Protein CD46; TMA, thrombotic microangiography	

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

The purpose of this chapter is to provide an assessment of whether eculizumab represents value for money for the NHS in England. The principal source of evidence used to inform this is the MS[1] to NICE, which includes a fully executable cost-consequence model and a written description of the methods and results of an economic analysis using the manufacturer's model. A key element of this chapter involves a detailed exposition and critique of this model and associated economic analysis. In addition, wider consideration is given to other economic analyses of eculizumab for the treatment of aHUS available either from the literature or elsewhere in the public domain. Given the concerns of the ERG with respect to the credibility of the submitted manufacturer's model, Chapter 6 includes exploratory analyses undertaken using a new model developed by the ERG; this exploratory analysis, as far as possible, retains the manufacturer's choices regarding the use of evidence sources, assumptions and general model structure and assumptions, but rectifies the mathematical irregularities and inappropriately restrictive assumptions within the manufacturer's model with the intention of providing a more robust and useful basis for informing decision-making.

5.2 Review of existing economic analyses

The MS[1] includes the details of a systematic review of economic evaluations of eculizumab for the treatment of aHUS (MS page 129). The submission states that no economic evaluations in aHUS patients were identified through their systematic searches. Although the ERG noted problems with the searches used by the manufacturer (see Section 4.1), it is unlikely that any published economic evaluations of eculizumab for aHUS have been missed by the manufacturer's search.

Whilst the manufacturer's review did not identify any published economic evaluations of eculizumab for the treatment of aHUS, it should be noted that the grey literature *does* include relevant evidence relating to the cost-effectiveness of eculizumab versus standard care for the treatment of aHUS in England.

In August 2013, NHS England published a clinical commissioning policy statement[29] which outlines arrangements for eculizumab to be made available for patients with aHUS whilst NICE guidance is being developed. This commissioning document cites an analysis of the costs and benefits of eculizumab as well as incremental cost-effectiveness ratios (ICERs) for eculizumab versus standard care, produced by the manufacturer, of £521,000 per QALY gained for a 23-year old cohort of patients and £376,000 per QALY gained for a 2-year old cohort of patients.[29]

The ERG believes that the existence of this previous model should have warranted some discussion within the MS as it reports information directly relevant to the expected incremental health benefits and costs of eculizumab versus standard care for the treatment of aHUS.

5.3 Exposition of the manufacturer's model

5.3.1 Economic evaluation scope

The manufacturer's submission to NICE presents a model-based cost-consequence analysis using QALYs for eculizumab versus standard care for the treatment of patients with aHUS. The analysis takes the perspective of the NHS in England but does not include potential costs which may fall on Personal Social Services (PSS). The model estimates costs and consequences for a 28-year old population over a lifetime horizon; this involves the extrapolation of costs and health outcomes for the hypothetical model cohort for up 125 years (although virtually all patients have died considerably earlier than this point). The primary outcomes generated by the model are the estimated incremental QALY gain and the incremental costs associated with the use of eculizumab compared against standard care. The manufacturer's model also estimates intermediate outcomes including ESRD-free survival and overall survival, both of which are used to estimate the total QALY gains in each treatment group. Costs and health outcomes are discounted at a rate of 1.5%. For those patients receiving eculizumab, treatment dosage is assumed to be dependent on bodyweight for paediatric patients, whilst a fixed dose is assumed for adults; this is in line with the current EMA licensed indication for eculizumab.[24] Upon starting treatment with eculizumab, it is expected that patients will remain on eculizumab indefinitely for the rest of their lives; this is the only treatment scenario reflected in the model. Within the standard care group, the main treatment option is assumed to be plasmapheresis, although it is assumed that a proportion of patients will undergo kidney transplantation if and when they progress to ESRD; transplantation is therefore considered to be part of the treatment pathway rather than a treatment option in its own right. Dialysis is modelled for patients in ESRD. Liver-kidney transplantation is not considered either as a comparator or as part of the treatment pathway in either treatment group. The different dosage regimens for the intervention and comparator groups are presented in Table 18.

Table 18: Competing treatment options included in the manufacturer's health economic model

Treatment group	**Dose / frequency**		
Eculizumab	**Body mass**	**Induction dose**	**Maintenance dose**
	Patients < 18 years of age		
	5kg to <10kg	300mg weekly x 1 dose	300mg at week 2; then 300mg every 3 weeks
	10kg to <20kg	600mg weekly x 1 dose	300mg at week 2; then 300mg every 2 weeks
	20kg to <30kg	600mg weekly x 2 doses	600mg at week 3; then 600mg every 2 weeks
	30kg to <40kg	600mg weekly x 2 doses	900mg at week 3; then 900mg every 2 weeks
	≥ 40kg	900mg weekly x 4 doses	1200mg at week 5; then 1200mg every 2 weeks
	Patients ≥ 18 years of age		
		900mg weekly x 4 doses	1200mg at week 5; then 1200mg every 2 weeks
Plasma therapy	1.5 times expected plasma volume (equivalent to 60-75mL/kg body weight). Once per week		

5.3.2 Model structure

The model is intended to simulate the experience of patients with aHUS receiving eculizumab or standard care principally in terms of the progression of kidney damage (defined as severity of CKD) and its impact in terms costs, HRQoL and survival. The model is implemented using a Markov cohort approach and is comprised of five mutually exclusive health states. At any point in time, all patients in the modelled cohort must reside in one of these five states. Three of the model health states reflect the patient's level of kidney function (CKD0-2, CKD3-4 and ESRD), a temporary health state for those patients who undergo a kidney transplant, and a dead state. The transplant health state represents a tunnel health state as patients only remain in this state for one cycle after which they transit to either CKD3-4 if their transplant was successful, or back to ESRD if their transplant was unsuccessful. The dead state represents an absorbing state and virtually all patients eventually transit to this state by the end of the modelled time horizon. The level of kidney function is defined in terms of CKD stage which is in turn directly determined by the estimated glomerular filtration rate (eGFR) and the level of kidney damage of patients (see Table 19). The model is divided into equal increments of time with a cycle length of 6-months; during each Markov cycle, patients transit between the five model health states based on time-independent matrices of transition probabilities. Spending one model cycle in each health state is associated with a specific level of HRQoL and costs associated with treatment and monitoring. The model does not assume either health losses (disutilities) or costs associated with transitions between health states. The same health states apply to both the eculizumab and standard care groups; the use of different allowed transitions between states and different

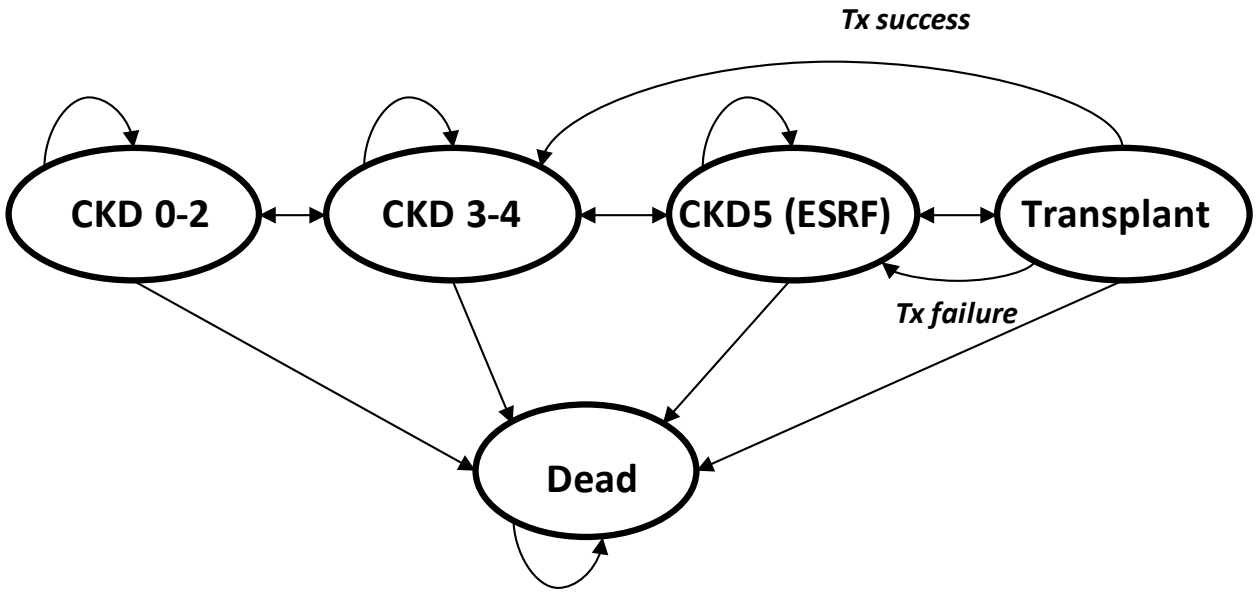
transition probabilities between states results in different trajectories through the model and hence different costs and health outcomes between the two treatment groups.

Table 19: Relationship between eGFR and CKD stage

CKD stage	eGFR	Banded CKD state used in manufacturer's model
1	90+	CKD0-2
2	60-89	
3a	45-59	CKD3-4
3b	30-44	
4	15-29	
5	<15 or on dialysis	ESRD

A conceptual representation of the model health states and possible transitions for the eculizumab and standard care groups within the implemented health economic model are presented in Figure 1. Whilst the model structure is the same for the eculizumab and standard care groups, it is assumed that patients receiving eculizumab will not undergo transplantation hence these transitions do not apply to the eculizumab group. It should also be noted that whilst the transition probabilities are estimated according to individual CKD state (0, 1, 2, 3a, 3b, 4, 5) for both treatment groups, these are subsequently condensed down to bands of CKD states in order to estimate health impacts and costs (CKD0-2, CKD3-4, CKD5/ESRD).

Figure 1: Conceptual representation of the manufacturer's model*



**note – not all transitions are allowed for standard care*

Upon entry into the model, patients are initially distributed across the CKD and ESRD disease states based on the distribution of patients at the beginning of the two completed prospective eculizumab studies (studies C08-002A/B and C08-003A/B). These data are naively pooled without any form of statistical adjustment for potential heterogeneity between studies. The results of the other eculizumab studies included in the MS[1] (studies C09-001R, C10-003, C10-004, C11-003, M11-001) were not used to inform the model parameters. No rationale is given with respect to the exclusion of data studies C10-003 and C10-004 within the model. The model population is somewhat confusing as the Markov state membership clearly indicates that the population enters the model at age 28 years, yet the costing assumptions imply a population in which 60% of patients are adults and 40% are paediatric patients. A single set of treatment-specific CKD transition probabilities is used for the entire duration of the model time horizon for each of the treatment groups. The risk of death is assumed to vary by age band (one 5-year band until age 5 and 10-yearly bands thereafter) and the overall transition probabilities are adjusted in each band to produce time-dependent transition probabilities which reflect a differential rate of death by age.

For the eculizumab group, transitions to better or worse health states are possible during any model cycle. In the standard care group, only transitions to worse health states are possible except when transplantation is assumed to be successful, whereby the patient is assumed to return to CKD state 3a (thus they return to banded state CKD3-4). Transitions to the transplant health state are assumed to be relevant only to the standard care group. Within the standard care group, an excess risk of death over and above all-cause mortality is assumed to apply to all health states and all model cycles; this excess death risk differs between the ESRD/transplant states and the less advanced CKD states. Conversely, in the eculizumab group, an excess mortality risk is assumed to apply only for patients in the ESRD and transplant states, hence no additional risk of death over and above general population other-cause mortality is assumed for patients receiving eculizumab in states CKD0-4. Thus, if a patient treated with eculizumab does not develop ESRD, their survival is assumed to be identical to that of the general population. An age band-dependent and state-independent background mortality rate is also included in both treatment groups; this is used to account for patients who die from causes other than aHUS. Deaths may occur during any model cycle in both treatment groups.

Total QALYs gained in each treatment group are estimated as a function of the time spent in each living health state and the level of HRQoL associated with each state. Resources and costs associated with the group-specific treatments and the management of CKD are estimated in each group. The broad groups of resource costs included in the model are shown in Table 20:

Table 20: Resource cost components included in the manufacturer's model

Standard care group	Eculizumab group
Cost of managing CKD Cost of plasma therapy Dialysis costs Transplant costs	Cost of managing CKD Cost of eculizumab acquisition and administration Dialysis costs Cost of vaccination

The model thus makes the following key structural assumptions:

- Excluding the impact of death, rates of CKD progression are time-invariant for both treatment groups
- CKD status of patients receiving standard care cannot improve unless the patient receives a transplant
- Eculizumab-treated patients can improve or worsen in terms of CKD
- Eculizumab-treated patients never undergo transplantation yet ESRD can be resolved without transplant
- Eculizumab-treated patients have the same risk of death as the general population except if/when they develop ESRD
- Standard care patients suffer a constant additional risk of death due to aHUS irrespective of their level of CKD.

5.3.3 Evidence used to inform the manufacturer's model parameters

Table 21 presents a summary of evidence sources used to inform the manufacturer's model parameters. A full list of model parameter values and sources is presented in the MS[1] (Table D4, pages 147-152). Issues surrounding the derivation of model parameter values and the appropriateness of selected sources are discussed in Section 5.5.

Table 21: Summary of evidence sources used to inform key parameter groups in the manufacturer's model

Parameter group	Source of parameter values
Initial patient distribution	Studies C08-002 and C08-003 (treatment phase)[1]
Eculizumab CKD transition probabilities	Studies C08-002 and C08-003 (treatment phase)[1]
Standard care CKD transition probabilities	Studies C08-002 and C08-003 (pre-treatment phase)[1]
Probability patient undergoes transplant	Studies C08-002 and C08-003 (pre-treatment phase)[1]
Probability transplant is successful*	Legendre *et al*[39]
Excess death rate standard care (CKD0-4)	Model fitted to mortality estimates from Coppo *et al*[31]
ESRD excess death rate (both groups)	UK Renal Registry 15th Annual Report (2012)[77]
Transplant mortality rate	UK clinical expert opinion[1]
Other-cause mortality	Interim life tables[78]
CKD, transplant and dialysis costs	Black *et al*[79] and NHS Reference Costs 2011[80]
Eculizumab costs	BNF[25] and NHS Reference Costs 2011[80]
Plasmapheresis costs	NHS Reference Costs 2011/12[80]
CKD health utilities	Studies C08-002 and C08-003 (treatment phase)[1]

** The MS cites four studies here but only actually uses estimates from Legendre et al[39]*

5.3.3.1 Relative treatment effects of eculizumab versus standard care

It is important to be clear from the outset that there does not currently exist any direct comparative evidence concerning the relative clinical effectiveness of eculizumab versus current standard treatments such as plasma therapy or transplantation (see Chapter 4). Whilst most Markov models would typically apply a relative hazard ratio to an underlying rate of transition between health states, or apply a relative risk to a transition probability within a particular time interval, such information is not available for eculizumab versus any other intervention from a single comparative source (i.e. an RCT). As a consequence, the model applies transition probabilities for the eculizumab group and standard care cohorts independently. The eculizumab CKD transition probabilities are based on changes between CKD state observed within prospective studies C08-002A/B and C08-003A/B, whilst the standard care transition probabilities are estimated using a fixed effects regression analysis of the rate of eGFR decrease observed within the pre-treatment phase of these same studies. Additional transition probabilities relating to aHUS-specific excess mortality risks from each state, probabilities of undergoing transplantation and probabilities of transplantation being successful were estimated from these studies and the wider literature.[31,39,77,77]

5.3.3.2 Transition probabilities for standard care

The CKD transition probabilities for the standard care group were calculated from retrospective data obtained from the 37 patients enrolled in studies C08-002A/B and C08-003A/B. According to the MS,[1] data were obtained from diagnosis to the start of the studies (however the ERG is not convinced that this is accurate, see Section 5.5). A regression analysis was conducted on reported eGFR observations to estimate a relationship between eGFR and the number of days on standard care

treatment (see MS[1] page 140). A fixed-effects model was used to estimate the eGFR decline per day. This model estimated a decline of 0.030 eGFR points per day which is reported to equate to a decline of 5.498 points over 182 days (6 months). Based on the manufacturer's stated assumptions that a decline of 15 eGFR points results in a decline of one CKD stage (see Table 19) and that patients are uniformly distributed across CKD stages, the manufacturers divided the eGFR interval width of 15 by 5.498 to give a 6-monthly transition probability of 0.367. This is assumed to reflect the transition from each individual CKD state to the next progressive CKD state during each model cycle. The remaining patients are assumed to remain in their current CKD state, undergo transplantation or transit to the dead state.

For patients in the ESRD state, the excess death rate was estimated using data on survival of patients on renal replacement therapy. The submission states that a probability of 5.1% per 6 months was calculated based on survival of 89.8% at one year.[77] It should be noted that in the model the actual probability used is 5.2%. An additional excess death rate is applied to all patients on standard care to account for the effects of additional, non-renal, complications of aHUS (see MS[1] page 133). For this risk, the manufacturer used data from the Coppo *et al* registry which gave a mortality rate of 13% at 18 months.[31] The excess death rate was then estimated using Solver within the model taking into account death from ESRD and background mortality to give an excess death rate of 4% per 6-month cycle; this excess mortality rate is applied each cycle to standard care patients in CKD stages 0-4.

The probability that a patient receiving standard care receives a transplant during any model cycle was estimated based on the number of transplants that occurred in the patients prior to entry into studies C08-002A/B and C08-003A/B. The MS reports that 25 transplants took place in 16 patients; a graphical summary of the timing of transplants was provided by the manufacturer in response to the ERG's clarification questions[34] (#48). The number of pre-treatment study days was calculated by multiplying the total number of patients (37) by 362. The total pre-treatment study days is then divided by 182 to give the total number of 6-month increments during the pre-treatment phase (71.56). The total number of transplants (25) is then divided by the number of 6-month intervals resulting in an estimated 6-month probability that a patient undergoes transplant of 0.349. This probability is applied to standard care patients in ESRD during each cycle.

The proportion of successful and unsuccessful transplants was based on the proportion of unsuccessful transplants at one year reported in Legendre *et al.*[39] Within this paper, this quantity was reported to be 0.60 to 0.90. The MS also references three other studies[81;22;11] however the range used is only reported in Legendre *et al* (see Section 5.5.2). The manufacturer's model assumes a midpoint value of 0.75 within the model. It should be noted however that this relates to a 1-year probability in

Legendre *et al* but is applied to each 6-month cycle in the model. Patients in whom transplantation is unsuccessful are assumed to return to the ESRD state after 6-months whilst patients in whom transplants are successful are assumed to regress to state CKD3a. This assumption was based on data from a large study of recipients of renal transplants where at one year 60% had CKD 3, 27% CKD 2 and 10% CKD 4 (the MS cites a study by Marcen *et al* however a full reference is not provided). Transplant mortality was based on UK clinical opinion that it would be *"at least as high as ESRD."*[1]

5.3.3.3 Transition probabilities for eculizumab

Transition probabilities for the eculizumab group were derived from the two prospective eculizumab studies (Study C0-002A/B and Study C08-003A/B) based on patient-level measurements of CKD stage at baseline, 6-months, 12-months, 18-months, 24-months, 30-months, 36-months, and 42-months. The manufacturers constructed Markov matrices for observed transitions between the seven CKD states (0, 1, 2, 3a, 3b, 4, 5) within each 6-month interval. Missing data were censored. The seven time-dependent CKD transition matrices were then combined into one single matrix weighted by the sample size of the non-missing values. The seven CKD states were then converted into the three CKD states (CKD0-2, CKD3-4, and CKD5) in the model. The single transition matrix is used for the entire duration of the model with adjustments for death from ESRD and background mortality, hence the observed time-dependent transitions between CKD states are applied in the model as if they are time-independent. As noted in Chapter 4, studies C0-002A/B and C08-003A/B were both non-randomised single arm studies and therefore did not compare the effectiveness of eculizumab directly with standard care or any other comparator. No excess death rate for non-renal complications of aHUS was applied to the eculizumab population. The MS states that one death occurred during the follow-up period of the two studies (C08-002A/B and C08-003A/B) due to gastrointestinal haemorrhage which was not related to eculizumab (see MS[1] page 86). On the basis of this observation, and with the exception of other-cause mortality, the model assumes a zero probability of transiting from CKD0-2 to death or from CKD3-4 to death and assumes a risk of death from ESRD based on the general death rate for all patients undergoing dialysis.[77] The submitted model also assumes that no patients on eculizumab would receive a transplant. Within the model, eculizumab is also assumed to have a treatment benefit in terms of reducing the frequency and severity of complications experienced; this is reflected in the use of different HRQoL valuations for the same state (see Section 5.3.3.4).

Tables 22 and 23 present the transition probabilities used in the model for each treatment group for comparison. Data sources, assumptions and use of expert opinion for each non-zero value are indicated in the table footnotes.

Tables 22: Eculizumab transition probabilities (excluding background mortality)

	CKD0	CKD1	CKD2	CKD3a	CKD3b	CKD4	ESRD	Transplant	Excess death
CKD0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CKD1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CKD2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CKD3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CKD3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CKD4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ESRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	0.05*
Transplant	-	-	-	1.00‖	-	-	-	-	0.05†
Excess death	-	-	-	-	-	-	-	-	1.00

**Expert opinion; † UK Renal Registry report;[77] ‖Assumption based on Marcen et al; all other non-zero values estimated from analysis of studies C08-002A/B and C08-003A/B*

Table 23: Standard care transition probabilities (excluding background mortality)

	CKD0	CKD1	CKD2	CKD3a	CKD3b	CKD4	ESRD	Transplant	Excess death
CKD0	0.59	0.37	-	-	-	-	-	-	0.04§
CKD1	-	0.59	0.37	-	-	-	-	-	0.04§
CKD2	-	-	0.59	0.37	-	-	-	-	0.04§
CKD3a	-	-	-	0.59	0.37	-	-	-	0.04§
CKD3b	-	-	-	-	0.59	0.37	-	-	0.04§
CKD4	-	-	-	-	-	0.59	0.37	-	0.04§
ESRD	-	-	-	-	-	-	0.60	0.35	0.05*
Transplant	-	-	-	0.25‖	-	-	0.70	-	0.05†
Excess death	-	-	-	-	-	-	-	-	1.00

**Expert opinion; † UK Renal Registry report;[77] ‡ Legendre et al[39] § estimated by fitting model to data reported by Coppo et al;[31] ‖Assumption based on Marcen et al; all other non-zero values estimated from analysis of studies C08-002A/B and C08-003A/B*

5.3.3.4 Health-related quality of life

The health utility values presented in the MS were drawn from EQ-5D data collected within studies C08-002A/B and C08-003A/B. EQ-5D scores from the two studies were measured during the studies and are reported at baseline, day 364 and at a median treatment duration of 62 weeks. EQ-5D values for CKD0-2, CKD3-4 and ESRD at day 364 were assumed to reflect the utility scores for patients receiving eculizumab (see Table 24, column 2). The difference between all scores at baseline and at the median treatment duration of 62 weeks was estimated to be 0.208; this value was used to characterise the difference between HRQoL for patients receiving standard care patients and for patients receiving eculizumab; this is applied as a disutility to all standard care CKD states (see Table 24, column 3). This results in the same health state being valued very differently for standard care patients and eculizumab patients; the MS indicates that this assumption was made to take account of the non-renal TMA events expected to cause substantial disability in the standard care group.[1] These values are applied for the entire duration of the modelled time horizon. EQ-5D utilities were valued

using the UK valuation tariff.[82] The utility within the transplant tunnel state is assumed to be the same as the utility for the standard care CKD3-4 state (value=0.662); this assumption is not mentioned in the MS.

Table 24: EQ-5D scores used within the manufacturer's model

Health State	Eculizumab	Standard care	Difference	Number of patients for observed EQ-5D score
Model state CKD0-2	1.00	0.792	-0.208	2
Model state CKD3-4	0.87	0.662	-0.208	24
Model state ESRD	0.867	0.659	-0.208	10
Model state Transplant	0.662	0.662	0.00	-

5.3.3.5 Resources use and costs included in the model

Cost of eculizumab

The dosing regimen for eculizumab is shown in Table 18. The acquisition costs for eculizumab were based on a list price of £3,150 per 300mg vial.[25] The acquisition costs of eculizumab for a 6-month maintenance cycle were therefore calculated to be £163,800 (52 vials) per patient. The initial induction treatment cost for eculizumab is higher, hence the first 6-month cycle is calculated to cost £176,400 (56 vials) per patient. Lower values were assumed for the costs of eculizumab in patients below the age of 13 years using weighting factors which make assumptions about the relationship between body mass and age. These costs are summarised in Table 25. [redacted] percent of the population is assumed to receive paediatric dosing at baseline, with [redacted] in each of the four bands shown in Table 25. Importantly, since patients enter the model at age 28 years, it is unclear why dose (and cost) reductions associated with paediatric patients are included in the model.

Table 25: Assumptions regarding age, body mass and eculizumab acquisition cost for paediatric patients

Body mass	6-month induction cost	6-month maintenance cost
5kg to <10kg	£31,500	£25,200
10kg to <20kg	£47,250	£40,950
20kg to <30kg	£88,200	£81,900
30kg to <40kg	£126,000	£122,850

Cost of managing CKD

Six-monthly costs of CKD management by CKD state were derived from an HTA study reported by Black *et al*;[79] these costs were assumed to be £960, £971 and £982 for states CKD0-2, CKD3-4 and

ESRD respectively. Black *et al* report costs for patients with differing levels of co-morbidities; the higher estimate was used in the manufacturer's model with the justification that patients with aHUS generally have a poor state of health. This was intended to represent the cost of managing a patient with CKD, a high albumin-creatinine ratio, and cardiovascular disease (CVD). The costs were inflated to 2010 prices using the NHS inflation indices published by the Personal Social Services Research Unit (PSSRU).[83]

Cost of plasma therapy

Alongside the costs of managing CKD detailed above, patients in the standard care group also incur a cost of plasma therapy (plasmapheresis). Different costs are assumed for adults and paediatric patients; again, the justification for separate costs by age group is unclear as the cohort enters the model at age 28 years and is therefore adult by definition. The cost of plasmapheresis is applied each cycle to patients with CKD0-4 in the standard care group. This cost was estimated using NHS Reference Costs and the HRG code for "Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over" for adult patients and "Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 18 years and under" for paediatric patients. Using the upper quartile costs for daycase patients, these costs are assumed to be £599 per exchange for adults and £870 per exchange for children. This was multiplied by 52 weeks to give the annual cost of £31,148 for adults and £45,240 for children based on an assumption of one exchange per week. Expert advice received by the ERG indicates that this may be an underestimate. The values in the MS differ slightly (page 152) whereby the adult cost is reported to be £31,152 and the paediatric cost is reported to be £45,217. The use of the upper quartile of the unit cost was justified in the MS on the basis that aHUS patients require a larger volume of plasma to be infused than is typical in other patient groups undergoing plasma exchange and that aHUS patients require whole plasma to be used. The ERG believes that this is likely to be reasonable.

Costs of dialysis

All patients in the ESRD state are assumed to receive dialysis. The cost of dialysis was estimated using NHS Reference Costs[80] for each dialysis session and frequency information from NICE clinical guidance on dialysis.[84] All HRG codes for haemodialysis and peritoneal dialysis were used and weighted according to activity levels, costs and frequency. Haemodialysis was estimated to occur three times per week and peritoneal dialysis once daily.[84] Weighting the costs according to these frequencies produces an annual cost of £23,300 for adults and £38,945 for patients aged 18 years and younger; only the adult cost is implemented in the base case analysis.

Transplant costs

The costs for transplanted patients include the cost of the transplant and the costs of immunosuppressants. The cost of transplantation was taken from the NHS Reference Costs[80] where all 19 years and over HRG codes for kidney transplant were weighted according to activity level; this gives a value of £18,792. The ongoing annual cost following transplantation was estimated to be £6,641; this was taken from NICE Technology Appraisal 85.[85] It should be noted that the ongoing cost for immunosuppressants is only applied for successful transplant patients for the first 6-month cycle following transplant; this cost is not applied during any subsequent cycles.

Administration costs

For 80% of patients the cost of administering eculizumab is assumed to be borne by the manufacturer under the aHUS Homecare Initiative. It is unclear within the MS why this service will apply only to 80% of patients or how they will be identified. Few details of this scheme are provided within the MS. For the remaining 20% of patients, the cost is estimated using a cost of administration from NHS Reference Costs[80] ("Deliver Simple Parenteral Chemotherapy at First Attendance") which the manufacturer records as £197. This unit cost is multiplied by the number of administrations per 6 months in the maintenance period (13) to give a total of £2,561 for administration per 6 months. This cost is applied to 20% of the eculizumab population, thus giving a total NHS cost of £512.20 per 6-months on treatment.

Additional costs

The model includes a once-only cost of meningococcal vaccine for patients in the first cycle that they receive eculizumab. The cost of the meningococcal vaccine (£30) was taken from the BNF.[25]

5.3.4 Model evaluation

The results of the health economic analysis are presented in terms of the incremental QALYs and incremental costs for eculizumab versus standard care. Whilst the model includes a probabilistic sensitivity analysis (PSA) sampling routine, the headline results presented in the manufacturer's submission report and model are based on point estimates of all parameters rather than the expectation of the mean. The results of the PSA are not presented in the context of decision uncertainty, and do not make reference to a willingness-to-pay threshold.

Within the manufacturer's PSA, the following groups of parameters are sampled:

- Initial patient distribution
- Eculizumab CKD transition probabilities
- Standard care CKD transition probabilities
- Probability patient undergoes transplant
- Probability transplant is successful
- Excess death rate standard care (CKD0-4)
- ESRD excess death rate both groups
- CKD, transplant and dialysis costs
- CKD health utilities

In several instances, standard errors for uncertain distributions appear to have been assigned arbitrarily. Correlation between uncertain parameters (e.g. transition probabilities) is not considered within the analysis. Other-cause mortality, plasmapheresis costs and eculizumab acquisition and administration costs are held fixed at their point estimates. The visual basic code within the model is programmed to run 500 probabilistic samples.

In addition to the probabilistic analysis, the MS includes the results of a number of simple one-way and multi-way deterministic sensitivity analyses (see Box 3). It should be noted that the model is not programmed to automatically conduct these simple sensitivity analyses, hence the ERG have not attempted to replicate these but have instead reproduced the results presented in the MS (see Section 5.4).

Box 3: Simple sensitivity analyses presented within the MS[1]

Simple one-way sensitivity analyses

- Patient age at model start = 46 years
- Patient age at model start = 12 years
- Discount rate health outcomes and costs = 3% and 1.5% respectively
- Discount rate health outcomes and costs = 3% and 3% respectively
- Study population C08-002A/B only
- Study population C08-003A/B only
- Eculizumab ESRF death probability reduced by 50% (0.026/cycle)
- Standard care excess death probability increased by 50% (0.06)
- Standard care excess death probability increased by 50% (0.02)
- Standard care eGFR decline rate increased by 50% (0.55/day)
- Standard care eGFR decline rate increased by 50% (0.183/day)
- Standard care transplant success probability increased by 50% (0.375)
- Standard care transplant success probability reduced by 50% (0.125)
- Standard care transplant excess mortality probability increased by 50% (0.076)
- Standard care transplant excess mortality probability decreased by 50% (0.025)
- Health state costs increased by 50%
- Health state costs reduced by 50%
- Eculizumab price increased by 10% (£3,465)
- Eculizumab price reduced by 10% (£2,835)
- Plasmapheresis cost increased by 50% (£23,361)
- Plasmapheresis cost reduced by 50% (£7,787)

Multi-way sensitivity analyses

- Scenario 1: Age 45 at baseline, standard care health utility difference versus eculizumab +50%, eGFR decline -50%
- Scenario 2: Eculizumab reduces ESRF death likelihood by 50%, 3% discount rate on costs, eGFR decline +50%

** The ERG is unclear what these analyses represent or how they were implemented within the model*

5.4 Headline results reported within the manufacturer's submission

This section summarises the results presented in the MS.[1] Figures 2 and 3 present the Markov traces over CKD bands for the eculizumab and standard care groups respectively.

Figure 2: Markov trace for the eculizumab group within the manufacturer's model[1]

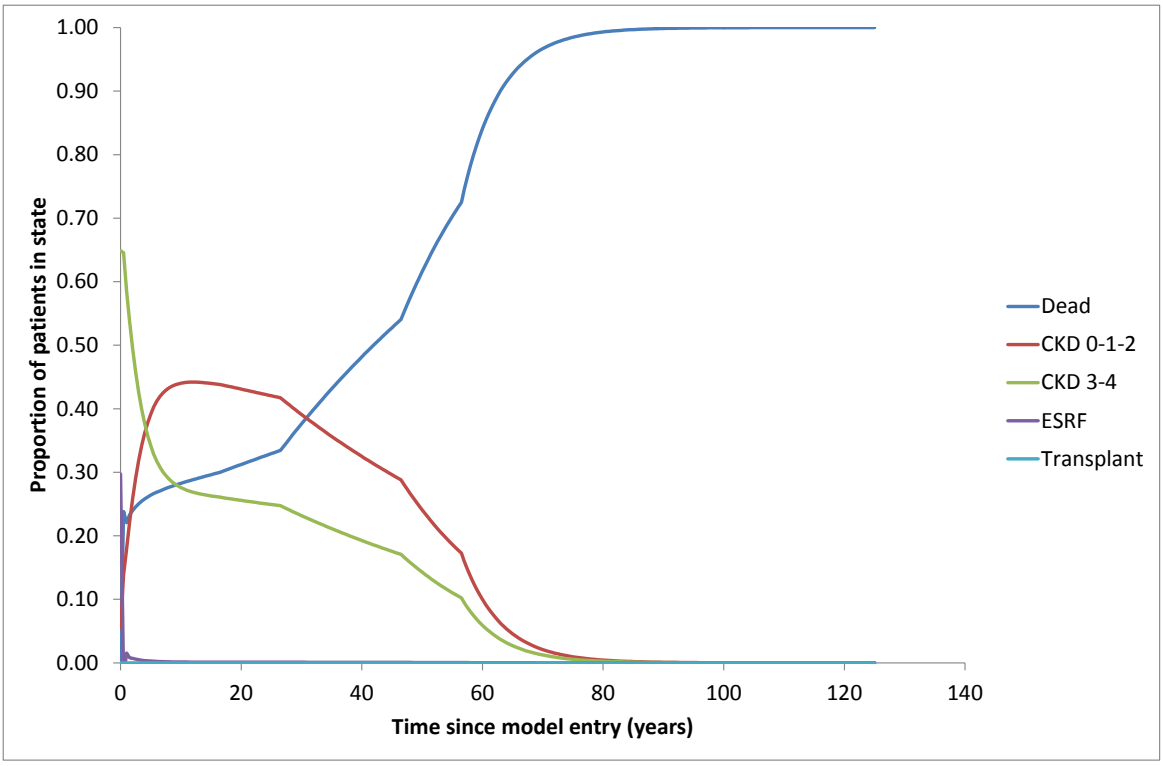
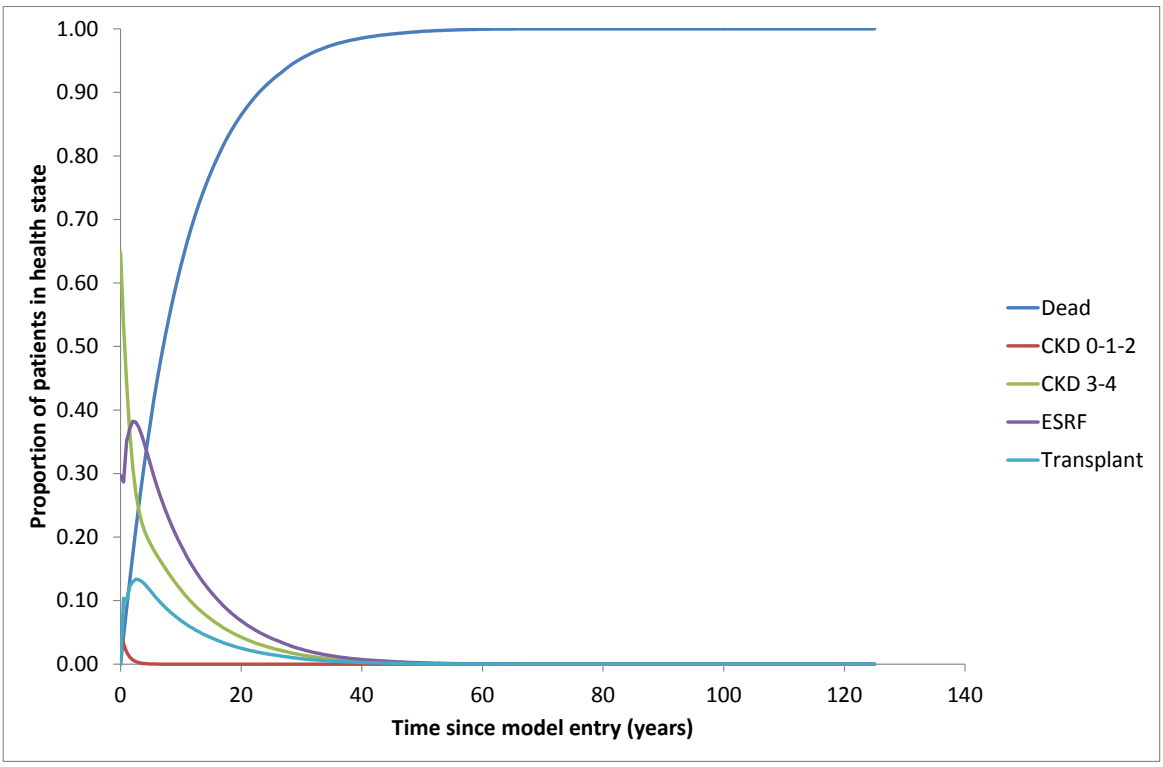


Figure 3: Markov trace for the standard care group within the manufacturer's model[1]



Figures 2 and 3 highlight the very good modelled prognosis for eculizumab patients and the very poor modelled prognosis for patients within the standard care group.

5.4.1 Headline total QALYs and total costs for eculizumab versus standard care

Table 26 presents the estimates of incremental QALYs and cost for eculizumab versus standard care. Without discounting, the manufacturer's model suggests that eculizumab produces an estimated 37.65 additional years of life and 38.47 additional QALYs compared to standard care per patient. The absolute survival estimate for the eculizumab (47.62 life years) is similar to the life expectancy for a healthy 28-year old population (roughly 53 years using 2011 life tables); the only difference in survival arises from the increased risk of death applied to those eculizumab-treated patients whilst in ESRD. The undiscounted incremental cost of eculizumab versus standard care is estimated to be in excess of [redacted] per patient. When discounted at a rate of 1.5%, the manufacturer's model suggests that eculizumab produces an estimated 24.08 additional years of life and 25.22 additional QALYs compared to standard care per patient. The discounted incremental cost of eculizumab versus standard care is estimated to be approximately [redacted] per patient.

Table 26: Summary results – manufacturer's model

Outcome	Eculizumab	Standard care	Incremental
Undiscounted results			
LYGs	47.62	9.97	37.65
QALYs	45.06	6.59	38.47
Cost	[redacted]	£366,679	[redacted]
Discounted results (at a rate of 1.5%)			
LYGs	32.82	8.73	24.08
QALYs	30.99	5.77	25.22
Cost	[redacted]	£322,313	[redacted]

Tables 27 and 28 present a breakdown of discounted QALYs and costs for eculizumab and standard care. Between-group comparisons of state-specific QALY gains are difficult to interpret due to the different modelled survival profiles, prohibited transitions for eculizumab-treated patients and different valuations of HRQoL for the same CKD state between the two treatment groups. These results indicate that the majority of the modelled QALY gains for eculizumab are accrued by patients in the less advanced CKD states. Conversely, patients receiving standard care gain little health from the CKD0-2 state, but accrue comparatively more health from the other health states. Table 28 indicates that the vast majority of the additional cost between the two treatment groups is attributable to the acquisition cost of eculizumab.

Table 27: QALY breakdown – manufacturer's model (discounted at 1.5%)

QALY component	Eculizumab	Standard care	Incremental
CKD 0-1-2	18.82	0.04	18.78
CKD 3-4	11.67	2.04	9.62
ESRD	0.51	2.72	-2.22
Transplant	0.00	0.96	-0.96
Total QALYs	30.99	5.77	25.22

Table 28: Cost breakdown – manufacturer's model (discounted at 1.5%)

Resource cost	Eculizumab	Standard care*	Incremental
CKD 0-1-2	[redacted]	£2,435	[redacted]
CKD 3-4	[redacted]	£113,701	[redacted]
ESRD	[redacted]	£100,372	[redacted]
Transplant	[redacted]	£103,437	[redacted]
Transplant success, ongoing costs	[redacted]	£2,367	[redacted]
Eculizumab cost	[redacted]	£0	[redacted]
Total cost	[redacted]	£322,313	[redacted]

** Includes the cost of plasmapheresis*

5.4.2 Sensitivity analyses presented within the manufacturer's submission

Table 29 presents a summary of the probabilistic results as presented within the MS.[1] The results of the manufacturer's PSA indicate that given the characterisation of uncertainty within the model, eculizumab is consistently expected to produce large incremental QALY gains and considerably higher incremental costs compared to standard care.

Table 29: Probabilistic model results (based on those reported in the MS[1])

Outcome	Eculizumab	Lower 95% crI	Upper 95% crI	Standard care	Lower 95% crI	Upper 95% crI
QALYs	31	28.4	32.7	5.9	2.6	8.7
Cost	[redacted]	[redacted]	[redacted]	£328,986	£170,557	£650,831

Table 30 presents the manufacturer's simple sensitivity analysis, as reported within the MS.[1] These simple sensitivity analyses indicate that the estimates of incremental health benefit and incremental cost are particularly sensitive to assumptions about patient age and the use of discounting. It should also be noted that the manufacturer's sensitivity analysis does not include an analysis in which the same utility values are assumed for both treatment groups, nor does it include an analysis which reflects a discount rate of 3.5% for both costs and health outcomes.

Table 30: Sensitivity analysis results presented within the MS[1]

Parameter	Base case	Sensitivity analysis	Standard care costs	Eculizumab costs	Incremental costs	Standard care QALYs	Eculizumab QALYs	Incremental QALYs
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 C08-002A/B patients only	all	only 002	£319,595	[redacted]	[redacted]	5.726	31.868	26.142
Include C08-003A/B 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 analysis	Standard care costs	Eculizumab costs	Incremental costs	Standard care QALYs	Eculizumab QALYs	Incremental QALYs
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

5.5 Critical appraisal of the manufacturer's model

This section presents a critical appraisal of the economic analysis submitted to NICE by the manufacturer. This critical appraisal has been undertaken through a detailed scrutiny of the manufacturer's model and through comparison of this with the written exposition of this model within the MS.[1]

The main problems identified by the ERG within the manufacturer's economic analysis are summarised in Box 4; these issues are discussed in detail in the subsequent sections.

Box 4: Main problems identified within the manufacturer's economic analysis

(1) Concerns regarding the scope of the manufacturer's economic analysis
(2) Problems relating to the derivation of transition matrices for eculizumab and standard care
(3) Highly favourable assumptions for the benefits of eculizumab
(4) Use of a restrictive model structure
(5) Inappropriate handling of competing risks
(6) Inappropriate estimation of background mortality
(7) Inappropriate use of probabilistic sampling and use of deterministic model results
(8) Conceptually unclear model population
(9) Pooling of potentially heterogeneous study populations
(10) Presence of technical modelling errors

(1) Concerns regarding the scope of the manufacturer's economic analysis

The scope of the economic analysis is partially in line with the decision problem specified by NICE (see Table 31), however there are some important deviations and concerns relating to (i) adherence of the economic analysis to the agreed NICE scope; (ii) the definition of comparators; (iii) perspective of the economic analysis; (iv) synthesis of evidence on outcomes; and (v) the discount rate used in the economic analysis.

Table 31: Adherence to the principles of the Reference Case relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic analysis is generally in line with the scope developed by NICE
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Plasma therapy including the possibility of kidney transplant. Liver-kidney transplantation is not included either as a comparator or as part of the pathway. As noted above, advisors to the ERG believe that this exclusion is likely to be appropriate. Dialysis is included for patients in ESRD.
Perspective on costs	NHS and PSS	An NHS perspective was adopted.
Perspective on outcomes	All health effects on individuals	Patient health benefits are included.
Type of economic evaluation	Cost-effectiveness analysis analysis*	Incremental costs and benefits are assessed in the form of a QALY-based cost-consequence analysis.
Synthesis of evidence on outcomes	Based on a systematic review	The effectiveness of eculizumab is based on a pooled analysis of patient-level data from two prospective single-arm studies whilst the comparator was based on analysis of pre-treatment eGFR change from patients enrolled in the same two studies. Outcomes for both groups were augmented using other literature and expert opinion No systematic review was undertaken for the comparators.
Measure of health effects	QALYs	Health outcomes are valued in terms of QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	All empirical utility estimates are measured using the EQ-5D. Utility data from the prospective eculizumab studies were valued using the UK time trade-off (TTO) tariff. There are issues with respect to the EQ-5D valuations in each treatment group.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Costs and outcomes were discounted at 1.5%.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to QALY gains.

** The form of the evaluation is not stated within the interim HST methods guide*

(i) Deviations from the NICE scope

Chapter 3 of this report highlights a number of aspects of the MS which deviate from the final NICE scope.[30] Specifically, the most important deviations within the economic analysis relate to the specification of the population and the methods used to estimate the effectiveness of the standard care

comparator. Whilst the manufacturer claim that the analysis reflects a mixed population of adults and children, this has been implemented incorrectly and only an adult population is actually considered, albeit with artificially lower acquisition costs for eculizumab. In addition, the ERG does not believe that the standard care group has been populated using the best available evidence (see Section 4.4). These two issues represent key limitations of the MS; as a consequence, the ERG has concerns with respect to the credibility and robustness of the economic analysis presented within the MS.

(ii) Definition of interventions and comparators

The description of the relevant interventions and comparators is generally appropriate. It is noteworthy that within the model, the possibility of transplantation is restricted to isolated kidney transplants and assumed to be relevant only to patients receiving standard care; patients receiving eculizumab are assumed to never undergo transplantation. The model does not include the possibility of combined kidney-liver transplant in either treatment group; advisors to the ERG believe this latter assumption to be generally appropriate.

(iii) Perspective of the economic analysis

The perspective of the analysis is generally appropriate - the model includes costs borne by the NHS and benefits enjoyed by NHS patients. However, whilst PSS costs are discussed in the MS, these are not included in the cost-consequence analysis. This is inconsistent with the manufacturer's analysis of wider societal benefits which clearly includes non-NHS/PSS costs for carers.

(iv) Synthesis of evidence on outcomes

As noted in Chapters 3 and 4, the MS does not include a full systematic review of evidence relating to the effectiveness of plasma therapy or transplantation in patients with aHUS. Instead, the focus of the review elements of the MS relate to single-arm studies in which patients received eculizumab. The MS does include some details regarding other studies which provide information on the prognosis and outcomes of patients with aHUS based on four registry studies.[11,31-33] However, this information is not presented as a systematic review; as a consequence, it is unclear how relevant outcome data have been identified, or why they have largely been neglected from the economic model.

(v) Discount rates for costs and health outcomes

The interim NICE methods and process guide for highly specialised technologies does not specifically state a preferred discount rate. The manufacturer's model discounts all costs and health outcomes at a rate of 1.5%. The NICE Technology Appraisal Reference Case[86] states that outcomes should be discounted at 3.5%, but that other rates can be considered in sensitivity analyses. Within their written submission,[1] and their responses to the ERG's clarification questions[34] (question #39),

the manufacturer argues that the use of lower discount rates is appropriate given Section 6.2.19 of the NICE Technology Appraisal Methods Guide:[86]

"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"[86]

However, it should also be noted that Section 5.6.3 of the Methods Guide states:

"*Sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis (see section 6.2.19).*"[86]

In the absence of a clearer direction from the interim HST methods guide, the ERG believes that the model results should be discounted at a rate of 3.5% in the base case analysis; additional sensitivity analyses could have been presented using the lower rate in secondary sensitivity analysis. Whilst the MS does include further sensitivity analyses around discount rates, none of these specifically use the 3.5% rate.

Other elements of the economic analysis related to the scope of the cost-consequence analysis

The use of a QALY-based cost-consequence analysis, in which costs and health benefits could be synthesised into an ICER, is appropriate in order to consider the balance of the additional value of eculizumab and the opportunity costs of the decision. The EQ-5D was consistently used to measure HRQoL impacts, albeit with small numbers in each model state; these were valued using the UK tariff.[82]

(2) Problems relating to the derivation of transition matrices for eculizumab and standard care

The absence of direct head-to-head RCTs assessing eculizumab versus any other comparator leads to considerable difficulties in estimating the comparative effectiveness of eculizumab. All of the clinical evidence for eculizumab presented within the MS[1] is drawn from single-arm non-randomised studies. This problem is further compounded by the limited number of studies which have estimated the effectiveness of plasma therapy which is taken to represent the mainstay of treatment in the standard care group. In the absence of RCT evidence, some form of naïve indirect comparison must be undertaken against some other source. Within the economic analysis, the prognosis of patients in terms of kidney damage, survival and HRQoL is modelled using pooled patient-level data from two single-arm prospective eculizumab studies (studies C08-002A/B and C08-003A/B), whilst the prognosis of patients on standard care through the CKD states was estimated using regression

analyses of the pre-treatment phase of these same studies (prior to receiving eculizumab). The ERG has concerns about the validity of this comparison, the methods used to derive parameters describing the standard care trajectory, and the appropriateness of the manufacturer's decision *not* to use other aHUS registry data to characterise the trajectory of CKD damage for patients receiving standard care.

2a) Problems relating to the estimation of transition probabilities for patients receiving standard care

The standard care transition probabilities were derived from a retrospective collection of eGFR measurements in patients entering the prospective eculizumab studies C08-002A/B and C08-003A/B. Regression analyses were conducted to estimate the decrease in eGFR per day on standard care. The data available for analysis are panel data which measure eGFR over multiple time points. Four models were fitted to the data: ordinary least-squares (OLS) which does not account for within-patient correlation and does not use the multiple time points ("model a"), two mixed models (random intercept with common slope), one of which accounts for the within-patient correlation ("model b") and one which includes the addition of adjusting for the trial identity ("model c"). The final model ("model d") subtracts a patient's average eGFR score from the score at each time point. All models adopt a linear form.

In addition to these regression analyses (models a-d), a non-parametric LOWESS regression was used to examine whether the eGFR decline over time was approximately linear, although this analysis was exploratory and was not used directly within the model.

The outputs of the regression model are used to estimate the change in CKD stage based on the proportion of patients whose eGFR declined by 15 points per 6-month cycle. The fixed effects model produces a coefficient for eGFR worsening of 0.03/day; this coefficient was used in the cost-consequence model by transforming the coefficient into what the manufacturer states is a transition probability. The manufacturer's approach is detailed on page 143 of the MS:[1]

"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 m2) 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."[1]

This transition probability of 0.367 is used as the 6-month CKD progression probability between all individual consecutive worse states in the manufacturer's cost-consequence model.

The ERG has serious concerns with the manufacturer's approach to deriving the rate of eGFR decline and its application within the model. These concerns are discussed in detail below.

Problem 1: Issues surrounding the implementation and reporting of the regression analyses

Whilst the OLS model (model a) does not account for repeated measures, this regression model appears to have been applied correctly; however, the MS clearly recognises the violations of this model with regards to analysing panel data. This OLS model, the first mixture model (random intercept, fixed slope) and the fixed effects regression model (models a, b and d) each use pooled data from both trials which implicitly assumes that the two studies, and the patients recruited into them, are identical. No justification is given for this pooling. The second mixture model (model c) attempted to take into account that the data were drawn from two studies by including a dummy variable, although this is not handled appropriately. The model yields a common coefficient, β, for the number of days and the trial indicator variable, which adds an extra day to the number of days before baseline if the data arises from one of the two trials. When the dummy variable takes the value of zero, the model is fine, however when it takes the value of 1, the model becomes $eGFR_{it} = \alpha + \beta(days_{it} +1) + u_{it} + e_{it}$. In this situation, the model will arbitrarily add an extra day to the number of days before baseline; this is incorrect and will produce erroneous model results. It would have been more appropriate to define two unique parameters, β_1 and β_2. A more appropriate model specification would thus be $eGFR_{it} = \alpha + \beta_1(days_{it})+\beta_2(trial_{it}) + u_i + e_{it}$.

The manufacturer's interpretation of a fixed effects model (model d) seems to be correct but is not clearly explained within the MS, in particular with respect to how the model accounts for patient characteristics.

The manufacturers state that for any missing data in patients receiving dialysis, eGFR measurements are assumed to take a value of 10; however, this seems an arbitrary choice. The graph of the applied LOWESS regression indicates a considerable amount of missing data (the data suggest a lot of values of eGFR=10); this crude imputation approach may skew the results of the regression models. It would have been preferable to explore scenarios in which a more sophisticated multiple imputation approach was used and no imputation was used to examine whether cases are systematically missing and not missing at random.

The manufacturer does not report any form of formal model checking to assess the suitability of any of the four regression models. The ERG believes it would be appropriate to produce diagnostic plots and/or Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values to assist with model selection.

Whilst the manufacturer modelled the relationship between days on standard care and eGFR, they are actually interested in the relationship between days on standard care and CKD stages. A regression approach based on CKD stage would likely be more appropriate.

Problem 2: CKD states do not have equal eGFR widths

Table 19 shows the relationship between eGFR and CKD stage. For patients in CKD Stage 3a and below, a decline of 15 eGFR points would result in a change in CKD stage. However, this is not the case for patients in CKD Stage 2 and above; a patient with CKD 2 would require a decline of 30 eGFR points to incur a change in CKD stage. In other words, the width of the interval is not the same across all CKD states. As 5.4% of patients enter the model in CKD 2, the model is likely to overestimate the rate of decline in CKD stage in these patients.

Problem 3: Inappropriate interpretation of regression results

The estimated rate of change was -0.03 points/day which according to the MS, given a 15-point interval in each CKD band, leads to a transition probability of 0.367. This value is based on the logic that assuming that the eGFR rate is constant (i.e. a linear relationship between eGFR progression and time) patients will progress by -0.03 points each day for 182.5 days in the 6-month Markov cycle, and that this total eGFR worsening can be divided by the CKD interval width to give a 6-month probability ([0.03 x 182.5]/15). However, this appears to reflect some confusion between the quantities being estimated: the eGFR regression approach adopted by the manufacturer is not estimating a probability of transiting between states - it is estimating the probability of picking a patient in a given 15-point eGFR interval who is eligible to move to the next interval. It is further noteworthy that if the estimated rate of decline had been -0.10 or lower, this would lead to a 6-month probability which is greater than 1.0. This is clearly mathematically invalid and raises important questions regarding the validity of the manufacturer's approach.

In their response to clarification (question #32),[34] the manufacturer stated *"The boundedness issue is only a problem when we are close to 0% or 100%. In our case, it would require 12 times the standard error to reach the lower bound and 20+ times the standard error to reach the upper bound—which are likelihoods that are vanishingly small given the data."* The ERG believes that the fact that the probability does not exceed 1 is irrelevant; the issue is that it *could do* and the manufacturer's

approach is not estimating a transition probability. The methods used to derive transition probabilities are mathematically incorrect and the results of a model based on these methods should be approached with considerable caution.

Problem 4: Failure to formally test non-linear models

The manufacturer undertook standard linear regressions for panel data to estimate the decline in eGFR while on standard care using the available data from studies C08-002A/B and C08-003A/B. The ERG would argue that because eGFR is bounded at zero, a standard linear model cannot possibly be appropriate and models for bounded data should have been explored. The manufacturer notes this as a limitation. Aside from the issue of a zero bound, the question of whether the relationship is linear or not would be best addressed by formally comparing polynomial functional forms with the linear one. This would be done using formal statistical tests of significance and of model misspecification. The approach that has been presented by the manufacturer, using a LOWESS regression plot (see Figure 4) is of very limited value. The shape of the LOWESS line is very sensitive to the chosen bandwidth and several different bandwidths would therefore be required for this to be informative.

Figure 4: LOWESS regression analysis of eGFR over time

Problem 5: Appropriateness of the study population

The ERG also has concerns with respect to the use of the pre-study population used to inform the standard care CKD transition probabilities. The population contains only 37 patients, one of whom was diagnosed with Systematic Lupus Erythematosus (SLE) and was excluded from Study C02-008 (MS[1] page 86). However, the MS does not state that this patient was excluded from the pre-study population and implies that the pre-study population analysis was carried out on 37 patients. If a patient is excluded from the study it would be expected that they would also be excluded from the pre-study analysis. The ERG also is unclear regarding which patients were included in the pre-study population analysis. The MS states that "*the pre-treatment period was defined as the time from diagnosis to baseline in the trials*" (MS[1] page 140) and in the description of the eGFR measurements that "*the median interval between diagnosis and baseline was 186 days with a range of 965,1…*" (MS[1] page 140). However, in Table C8, which describes the population of studies C08-002A/B and C08-003A/B, the median time from diagnosis to screening was given as 9.7 months with a range of 0.26-236 months for study C08-002A/B and a median of 48 months with a range of 0.66-286 months for study C08-003A/B. This is also reflected in the transplant data provided by the manufacturer as part of the clarification process. Taking the largest in the range for both studies would result in measurements for 19 and 23 years not the 3 year maximum given in the range for the pre-study analysis. Both medians given in Table C8 for time from diagnosis to screening are longer than the median given for the per-study analysis which means that some patients and/or some observations for patients are missing. The median for study C08-003 of 48 months is far longer than the median given for the pre-study analysis of 186 days, indicating that many observations and/or patients with a longer length of time from diagnosis have been excluded from the regression analysis. However, the MS offers no explanation on which patients or which patients observations have been excluded and at no point states that any patients or observations have been excluded. The exclusion of either patients with long standing aHUS or observations from earlier in their disease process may bias the results of the regression analysis.

Problem 6: Relevant registry data exist but are not used within the economic analysis

The ERG is aware of larger longer-term registry studies that could have been used to estimate CKD damage in aHUS patients over time (see Tables 14 and 15). Due to the concerns raised above about the number of patients included in the analysis, the uncertainties regarding which patients were actually included, and the relatively short pre-treatment period, the ERG believes that aHUS registries[11,32] would have represented a considerably more relevant and appropriate source through which to estimate the standard care transition probabilities.

Problem 7: Issues relating to the calculation of the probability of undergoing transplant

The model assumes that transplant is possible only for those patients receiving standard care. The MS states that 25 transplants were undertaken in 16 patients during the pre-treatment phase of studies C08-002A/B and C08-003A/B. The model assumes a 6-month transplant probability of 0.349. This value was estimated by the manufacturer by dividing the number of transplants by the total number of 6-month increments during the pre-treatment period. In the model, this is calculated by multiplying 352 by 37 (the total number of patients in studies C08-002A/B and C08-003A/B). The ERG requested further information about these values as part of the clarification process; the manufacturer provided a figure showing the timing of transplantation in these 16 patients; this is reproduced in Figure 5.

Figure 5: Time of diagnosis and transplant during studies C08-002A/B and C08-003A/B[34]

[redacted]

Inspection of this figure indicates that [redacted]. However, the ERG notes that [redacted]. Using the figure provided by the manufacturer, the ERG estimate that across the 16 patients who received a transplant, the total pre-treatment period in which transplants took place was [redacted]. This gives a [redacted] 6-month probability of

transplant of approximately [redacted]. This calculation approach is likely to be further incorrect as the total pre-treatment time may include time in less advanced CKD states. The correct approach would involve calculating the probability of transplant conditional on the time spent in ESRD. Without knowing the proportion of pre-treatment time spent in ESRD, it is not possible to accurately estimate the 6-month probability of undergoing a transplant.

Problems relating to post-transplant outcome

The MS gives four references for the probability of as unsuccessful transplant. However, it would appear that only the range given in Legendre *et al*[39] (60-90%) is used to inform the parameter value of 75%. The other three references given in the manufacturer's submission give lower or larger ranges for the probability of an unsuccessful transplant.[81;22;11] The study by Le Quintrec *et al*[81] reported 50% graft loss at 5 years whilst the study by Zuber *et al*[22] found that aHUS recurrence and subsequent graft loss depended on the genetic mutation and rates of aHUS recurrence ranged from 15% to 100%.[22,81] The study by Noris *et al*[11] also found that graft loss differed depending on the genetic mutation; rates of graft loss ranged from 0% to 71% at one year; overall the study found that 55% of adult patients and 67% of the paediatric patients experienced graft loss at one year. Successful transplants recipients in the model are assumed to move to stage 3a. This was based on the outcomes from a large study of recipients of renal transplants where the majority (60%) were in CKD 3 at one year. The MS also reports that 27% of patients were in CKD 2 and 10% were in CKD 4 at one year (Marcen *et al* 2010, no reference provided in the MS). It is unclear why this re-distribution of patients was not applied for successful transplant recipients.

2b) Problems relating to the estimation of transition probabilities for patients receiving eculizumab

The manufacturer's model appears to include highly favourable transition probabilities for eculizumab. The same set of transition probabilities are used for the entire model duration. The ERG believes this to be inappropriate as that the empirical evidence appears to suggest that eculizumab offers an initial improvement in eGFR which is generally sustained over a longer period, rather than continual improvement in eGFR as assumed in the model. Based on the states used in the manufacturer's model (CKD0-2, CKD3-4 and ESRF), Table 32 presents a summary of those patients who improved, worsened or remained in the same banded CKD state between each 6-month interval. Figure 6 compares the observed and modelled CKD state membership over time.

Table 32: Summary of improved/worsened transitions for evaluable patients during each 6-month interval from studies C08-002A/B and C08-003A/B

Timepoint (months since baseline)	Number of patients with changed/same banded CKD state during 6-month interval			Number of patients in banded CKD state at timepoint			Total number of evaluable patients
	Improved state	Same state	Worsened state	CKD0-2	CKD3-4	CKD5	
0 months (baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unsurprisingly, given the assumption of time-independent transition probabilities, the model does not provide a particularly good fit to the observed data. The data presented in Table 32 and Figure 6 appear to indicate a substantial improvement in CKD state during the first 6-months on eculizumab; however, a similar magnitude of improvement is *not* evident at later timepoints. Rather, the data appear to indicate general stabilisation (with some improvement and some worsening) beyond the first 6-months of treatment.

Figure 6: Observed and modelled CKD state over the first 3-years

[redacted]

[redacted]

This view is further supported by the paper reported by Legendre *et al.*[39] In this paper, the authors state: "*In trial 1 (C08-002), the improvements in the estimated GFR from day 0-28 were maintained from day 29 through the data-cutoff point, with no further increase…*". Legendre *et al*[39] also reported that in trial 2 (study C08-003), eGFR improved slightly from week 26 to week 60. At week six the mean eGFR increase was six and this increased to a mean eGFR of nine at week 60. However, the ERG does not believe that this small increase in one of the studies provides sufficient justification for the use of a single set of transition probabilities based on the assumption that eculizumab results in a constant indefinite improvement in eGFR.

In the manufacturer's model, no eculizumab-treated patients receive a kidney transplant whilst a probability for kidney transplant is included in the standard care transition probabilities. This contradicts part of the argument set out in the MS for the benefits of eculizumab over standard care. In Section 7 of the MS,[1] the manufacturer states: "*One of the 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 and organ transplant…*" (MS page 45). In addition, one patient in studies C08-002A/B and C08-003A/B did receive a transplant. Therefore, the validity of assuming that no eculizumab-treated patients receive transplant is questionable. It should also be noted that two patients discontinued study C08-002A/B due to a decrease of worsening of renal function. Both these patients discontinued the study in ESRD. One patient had started the study in ESRD and after an improvement to CKD4 had returned to ESRD before discontinuing. The other patient started the study in CKD4 but progressed to ESRD and lost their kidney transplant before discontinuing the study.[52]

The ERG is also concerned that the observations for the patient who received the transplant in either study C08-002A/B or study C08-003A/B have not been censored after the transplant. If the observations are not censored, the effectiveness of eculizumab represented in the transition matrices will be overestimated as improvements in renal state for this patient may be related to the transplant rather than eculizumab treatment.

(3) Highly favourable assumption for the benefits of eculizumab

The model assumes that eculizumab eliminates the non-renal complications of aHUS; this assumption is used to justify the different HRQoL values used for eculizumab patients and standard care patients (utility difference = -0.208 for standard care versus eculizumab) and the elimination of the excess death risk for eculizumab patients (4% for standard care, 0% for eculizumab). The eculizumab studies reported in the MS[1] include three deaths and a number of complications that may indicate that

treatment with eculizumab does not fully eliminate the risk of non-renal complications of aHUS. The MS lists neurological, cardiac, and gastrointestinal complications as non-renal complications of aHUS (MS page 33). The three reported deaths in the studies fall under the above categories: two deaths occurred in the retrospective study (C09-001r) and were "*related to cerebrovascular accident (stroke) and fatal carotid artery dissection…*" (MS page 105) whilst the third death occurred during the extension period of study C08-003 and was due to gastrointestinal haemorrhage. However, these deaths may reflect a continuation of damage caused by complications of aHUS before the patient started on eculizumab. Of the 37 patients in studies C08-002A/B and C08-003A/B, [redacted]. Even if these deaths and adverse events were not related to eculizumab, they may indicate that eculizumab did not eliminate all complications of aHUS or reverse all previous damage caused by complications of aHUS before treatment on eculizumab was started.

The manufacturer's model does not include any adverse events for eculizumab. All studies reported a number of treatment-related AEs. In study C08-002A/B 10 (59%) of patients reported a treatment-related AE with one patient experiencing a severe treatment-related AE of hypertension. In study C08-003, six patients reported treatment-related AEs and there were two cases of severe treatment-related AEs listed as peritonitis and vein disorder. [redacted]. Treatment-related AEs were not listed for study C09-001r but one case of meningococcal meningitis was reported.[1]

The use of the study-derived HRQoL values may also overestimate the benefit of eculizumab. The use of a value of 1.0 for the health state CKD 0-2 is higher than the UK general population EQ-5D norms[87,88] and given that it is based on the reported values of two patients may not be appropriate to use. In addition, the single arm design of the studies from which the HRQoL values are derived may have influenced the elicited EQ-5D values. For example, if a double-blind RCT design had been used then the difference in HRQoL values between the patients on eculizumab and those on the comparator treatment could have been used to estimate the additional HRQoL benefit of eculizumab. However, given the absence of randomisation and blinding within the prospective eculizumab studies, the considerable expense of eculizumab, and the absence of an alternative effective treatment

for aHUS, it is possible that some patients valued their health on treatment because they were receiving eculizumab rather than because the drug had a noticeable impact upon the patients' HRQoL. In the absence of comparative evidence, this possible explanation remains conjecture, however, it should be considered as a possible source of bias.

Given the evidence discussed above, the ERG indicates that the large HRQoL decrement applied to standard care compared to eculizumab-treated patients may not be plausible.

It should also be noted that the HRQoL values used for eculizumab-treated patients in ESRD are generally much higher than those used in previous NICE submissions (see Table 33), whilst the utility value for patients receiving standard care are generally slightly lower.

Table 33: HRQoL values used for ESRD in previous NICE submissions

NICE submission	Value	Source
Renal failure – home versus hospital haemodialysis (TA 48)	0.66 hospital haemodialysis 0.81 satellite haemodialysis	DeWitt *et al*[89]
Hyperparathyrodism – cinacalcet (TA 117)	0.6735 Weighted average*	DeWitt *et al*[89]
Organ preservation (renal) – machine perfusion and static storage (TA 165)	0.76 The difference between dialysis and function transplant	Greiner *et al*[90]
Eculizumab for aHUS	0.867 Eculizumab-treated patients 0.659 Standard care patients	MS[1]

**Based on UK average of 73% of patients receiving haemodialysis and 23% receiving peritoneal dialysis*

(4) Use of a restrictive model structure

Further to the issues identified above, the ERG has concerns with respect to the restrictive nature of the manufacturer's model structure. The previous model submitted to AGNSS[13] allowed for time-dependent transition probabilities in both treatment groups. This flexibility is not a characteristic of the model submitted to NICE. For both eculizumab and standard care groups, the model applies a single fixed transition matrix, thus structurally imposing an assumption that CKD transition probabilities in both groups are time-invariant (excluding mortality effects). This is a highly restrictive assumption that does not make the best use of the available evidence. Within the eculizumab group, the manufacturer estimates time-dependent transitions between CKD states but then produces a single time-independent transition matrix weighted by the number of observations at each 6-month timepoint. This is mathematically questionable and does not reflect the available evidence on the nature of the hazard of CKD progression over time. Within the standard care group, again a single CKD transition matrix is assumed; this does not reflect data from other sources e.g. the Noris *et al* registry analysis[11] in which the hazard of ESRD and death appear to be very high at the initial aHUS episode, but considerably lower thereafter (see Table 15). Irrespective of whether it is

appropriate to treat the hazard of CKD progression as being time-dependent or time-independent, the manufacturer's model structure does not allow this to be explored as it only includes a single matrix in each treatment group. This presents an important limitation of the model.

(5) Inappropriate handling of competing risks

Within both treatment groups, the model is implemented such that probabilities of events (CKD transition, transplantation, aHUS death or other cause-death) are treated as if they are independent. This leads to a total probability of experiencing all events being greater than 1.0. This is handled in the model using a "mortality-pull" which downweights all transitions by the probability of death in each cycle. This is an inappropriate way of handling competing risks as it does not account for conditionality between events. It also appears that this does not allow for very high death probabilities. For example, in the eculizumab group, if the excess death risk for patients in ESRD is arbitrarily inputted as 0.80 (cell X13 markov_ecu worksheet), the probability of remaining in ESRD becomes -0.377. This is mathematically impossible and raises further questions regarding the robustness of the manufacturer's model results.

(6) Inappropriate estimation of background mortality

Within the model, other-cause mortality is modelled using 6-month probabilities applied over (mostly) 10-year age bands. Within each year, the model calculates the 6-month rate of death and then calculates an overall probability of death within each age band weighted by gender. This is unnecessarily "blunt" since annual probabilities are available from the life tables. A more appropriate approach would have involved calculating the mortality rate for each age-year, and then transforming this to a 6-month probability applied each year using standard formulae.[91]

(7) Inappropriate use of probabilistic sampling and use of deterministic model results

Whilst the manufacturer's model includes a probabilistic sensitivity analysis routine, some of the model parameters are held fixed at their point estimates, whilst others are characterised using inappropriate distributions. Table 34 highlights a number of differences between how parameter uncertainty has been characterised in the manufacturer's model and how the ERG would recommend characterising this uncertainty. Overall, the ERG would argue that the probabilistic results presented by the manufacturer are unlikely to reflect the true uncertainty surrounding the incremental costs and QALYs associated eculizumab versus standard care.

Table 34: Actual and preferred characterisation of uncertainty surrounding model parameters

Parameter group	Distributions assumed within manufacturer's PSA	ERG preferred approach given nature of defined parameter	ERG comment
Initial patient distribution	Non-parametric bootstrap	Dirichlet with minimally informative priors[91]	Bootstrapping tells us about variability rather than uncertainty
Eculizumab CKD transition probabilities	Non-parametric bootstrap	Dirichlet with minimally informative priors[91]	Bootstrapping tells us about variability rather than uncertainty.
Standard care CKD transition probabilities	Normal	Beta	Normal distributions are not bounded by 0 or 1
Probability patient undergoes transplant	Beta	Beta	-
Probability transplant is successful	Uniform	Beta	Uniform distributions (with equal likelihood of any value within bounded range) are unlikely to reflect the true uncertainty around this probability parameter
Excess death rate standard care (CKD0-4)	Beta	Beta	The standard error appears to be arbitrarily defined. More complex calibration methods (e.g. Markov Chain Monte Carlo) could be used to fit this parameter
ESRD excess death rate both groups	Normal	Beta	Normal distributions are not bounded by 0 or 1
Other-cause mortality	Fixed	Fixed	This is probably reasonable
CKD, transplant and dialysis costs	Gamma	Normal/gamma	SEs appear to be arbitrarily defined
Eculizumab costs	Fixed	Acquisition cost fixed, uncertainty surrounding administration cost	The true costs of drug administration costs are uncertain
Plasmapheresis costs	Fixed	Normal/gamma	This parameter is uncertain and should be sampled within the PSA
CKD health utilities	Beta	Beta	Health utility for state CKD0-2 is held fixed. Uncertainty appears to be sampled using the standard deviation rather than the standard error.

(8) Conceptually unclear model population

The model population begins with a cohort of patients aged 28 years. This drives the time horizon of the model and the probability of dying due to other causes during each model cycle. However, the model also includes dose reductions for [redacted] patients who are assumed to be children upon entry into the model. These dose reductions are based on assumptions about the relationship between bodyweight and age (see Table 18). It is therefore conceptually inconsistent, if not uninterpretable, to model the prognosis of adult patients but to include dose-reductions for paediatric patients. It should

further be noted that studies C08-003A/B and C08-002A/B did not include any patients under the age of 12 years.

(9) Pooling of potentially heterogeneous study populations

The manufacturer's model uses simple pooling of patient-level data from studies C08-002A/B and C08-003A/B to inform transition probabilities for both treatment groups. The 2012 eculizumab safety and efficacy update[52] states:

[redacted]

Whilst the manufacturer reports simple sensitivity analyses using the individual study populations, it is unclear whether it is appropriate to pool these data.

(10) Presence of technical modelling errors

Aside from the problems outlined above (in particular, refer to the identified issues regarding handling conditional probabilities), the ERG noted a number of technical programming errors in the manufacturers model.

(i) Sum of standard care transition probabilities greater than 1.0

In the calculations for the standard care transition probabilities (cell X33, markov_SOC worksheet) there is a clear programming error in the calculation of the transition probability from transplant to ESRD. This error is caused by the probability of remaining in transplant being calculated as one minus the transition from transplant to CKD3-4 rather than one minus the sum of all other transitions. As a consequence, the sum of this row of transition probabilities exceeds 1.0.

(ii) Incorrect cell references for transplant death and ESRD death

Within the eculizumab group patients there is a programming error with respect to which risk of death is used for patients receiving transplant and for patients in ESRD. For transplant patients, the risk of death due to ESRD is used, whilst for patients with ESRD, the risk of death due to transplant is used. This does not affect the base case results as both probabilities are the same and no eculizumab patients are assumed to undergo a transplant. However, it does impact on the standard care transplant excess mortality rate (+/- 50%) sensitivity analysis as the eculizumab costs and benefits are both affected by this error (see Table 30).

(iii) Double-discounting of transplant costs

For the standard care group, the ongoing costs of transplants are discounted twice. In the 'markov_SOC' worksheet, the cost of immunosuppressants are discounted using the =PV() formula; these costs are then discounted again when applied to the number of patients receiving the treatment.

(iv) Underestimation of immunosuppressant costs

The costs of immunosuppressants for patients undergoing transplantation are applied only for one cycle for those patients in whom transplant is successful. This cost should be applied to the length of time that the patient's transplanted kidney survives. However, the manufacturer's model does not include the functionality to track which patients received a successful transplant, how long they remained alive or how long their transplanted kidney survived. Consequently, the costs of standard care are likely to be underestimated.

(v) Reporting errors

The sensitivity analysis presented in Table D21 of the MS[1] (also presented in Table 30 of this ERG report) includes analyses in which the price of eculizumab was increased/decreased by 10%. However, these analyses do not result in different costs from those presented in the base case. This is interesting to note as the MS states that the price increase and price decrease are one of three factors for which the model results are most sensitive (see MS[1] page 174).

5.6 Discussion of available evidence relating to value for money for the NHS and PSS

The focus of this chapter has been on the economic evidence for eculizumab submitted to NICE by the manufacturer. This manufacturer's analysis takes the form of a QALY-based cost-consequence model comparing eculizumab versus standard care. The manufacturer's model indicates that eculizumab is expected to produce an additional 37.65 years of life and 38.47 QALYs compared to standard care per patient. The undiscounted incremental cost of eculizumab versus standard care is estimated to be approximately [redacted] per patient. When discounted at a rate of 1.5%, the manufacturer's model suggests that eculizumab produces an estimated 24.08 additional years of life and 25.22 additional QALYs compared to standard care per patient. The discounted incremental cost of eculizumab versus standard care is estimated to be [redacted] per patient.

The ERG critique identified several problems relating to the manufacturer's cost-consequence model. The most important of these concerns relate to the restrictive structural assumptions of the model, the inappropriate interpretation of evidence relating to the benefits of eculizumab over time, the inappropriate use of evidence to characterise CKD damage for patients receiving standard care, the inappropriate method for handling competing event risks and the highly questionable choice of

relevant evidence used to characterise the prognosis of patients receiving standard care. Whilst some of these problems could be resolved easily within the existing model, other more serious programming issues cannot not be resolved within the manufacturer's model structure (in particular, the inappropriate approach used to handle competing risks). The resolution of these problems requires the development of a new model. Overall, the ERG has concerns regarding the suitability of the manufacturer's model structure, the integrity of the pre-model analysis and the robustness of the manufacturer's model results.

In order to address some of the problems identified within the critical appraisal of the manufacturer's economic analysis, the next chapter outlines the development of a new model which attempts to address those problems which can be resolved, whilst as far as possible, retaining the model structure, assumptions and evidence choices employed by the manufacturer.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

This chapter presents two groups of additional analysis. Firstly, based on the critique of the economic analysis presented in the MS (see Section 5.5), the ERG present a re-analysis of the manufacturer's model which corrects for some, but not all, of the technical programming errors identified. The extent to which this analysis resolves the problems with the manufacturer's economic analysis is however very limited and a number of more substantial errors cannot be fixed within the constraints of the manufacturer's model structure. To this end, the second set of analyses involves the development of a new ERG model which addresses the more serious problems relating to the handling of competing risks and inappropriate modelling of the prognosis of patients receiving standard care. It should be emphasised that whilst this latter model has been developed with the intention of providing a more robust basis for informing decision-making, it should also be considered exploratory.

6.2 Re-analysis of the manufacturer's economic analysis following the correction of technical programming errors

This section presents a re-analysis of the manufacturer's model which includes the correction of technical programming errors. It should be re-iterated that despite these corrections, the ERG do not believe that the manufacturer's model synthesises the best available evidence appropriately or uses an adequate model structure, hence its value in informing decision-making is questionable. The problems relating to mathematical inconsistency are still present in this model. As a consequence, the ERG believes that the results of this re-analysis should be given very little consideration. The following technical errors were corrected by the ERG.

- The standard care transplant transition probabilities were corrected
- Paediatric dose reductions were removed for eculizumab and plasmapheresis
- The model was amended such that the transplant death probabilities and ESRD death probabilities are drawn from the correct input cells
- The double-discounting of ongoing transplant costs was removed
- The discount rate for costs and health outcomes was amended to 3.5% (see final 3 rows of results presented in Table 35).

The results of this re-analysis are presented in Table 35; all estimates are based on point estimates of parameters rather than the expectation of the mean. Full details of amendments to the executable model are presented in Appendix 1.

Table 35: Revised results following ERG correction of technical errors within the manufacturer's model

Outcome	Eculizumab	Standard care	Incremental
Cost-consequence results (undiscounted)			
LYGs	47.62	10.07	37.55
QALYs	45.06	6.66	38.41
Cost	[redacted]	£354,757	[redacted]
Cost-consequence results (costs and outcomes discounted at 1.5%)			
LYGs	32.82	8.80	24.01
QALYs	30.99	5.82	25.17
Cost	[redacted]	£310,421	[redacted]
Cost-consequence results (costs and outcomes discounted at 3.5%)			
LYGs	21.99	7.55	14.44
QALYs	20.71	4.99	15.72
Cost	[redacted]	£266,407	[redacted]

The results presented in Table 35 show that the correction of the technical errors in the model does have some impact upon estimates of health outcomes and costs. Assuming a discount rate of 1.5%, the corrected estimate of incremental cost is [redacted] per patient. The corresponding estimate of incremental QALYs gained is also decreased from 25.22 additional QALYs to 25.17 additional QALYs.

6.3 Development of the exploratory ERG model

6.3.1 Summary of similarities to the manufacturer's model

In light of the more substantive problems with the manufacturer's model discussed in Chapter 5, the ERG developed a new model. This process was undertaken to allow the ERG to explore the likely impact of making more plausible assumptions about the nature of CKD event hazards over time and to more appropriately handle competing risks. This was not possible within the manufacturer's model. It should be noted that the rebuilt ERG model is identical to the manufacturer's model in terms of model structure, assumptions and evidence choices with the exception of six factors:

1. The transition probabilities for the eculizumab and standard care groups are allowed to be time-dependent. This was not possible in the manufacturer's model as only a single CKD transition matrix was applied within the model.
2. The risk of death is modelled using an iterative looping approach which conditions competing events at time *t* on the proportion of the population alive at time *t*. This was necessary as the manufacturer's model did not handle conditional probabilities appropriately, hence it was possible to produce negative transition probabilities; this problem could not be fixed in the manufacturer's model without adapting its structure.
3. The transition probabilities for the standard care group (CKD damage, transplant probability and mortality risk) are fitted to outcomes data reported at different timepoints by Noris *et al*.[11] This

amendment was made for two reasons: (i) the manufacturer's methods for estimating this quantity are mathematically incorrect (see Section 5.5), and (ii) registry data provide a more appropriate source of evidence for estimating standard care transition probabilities.

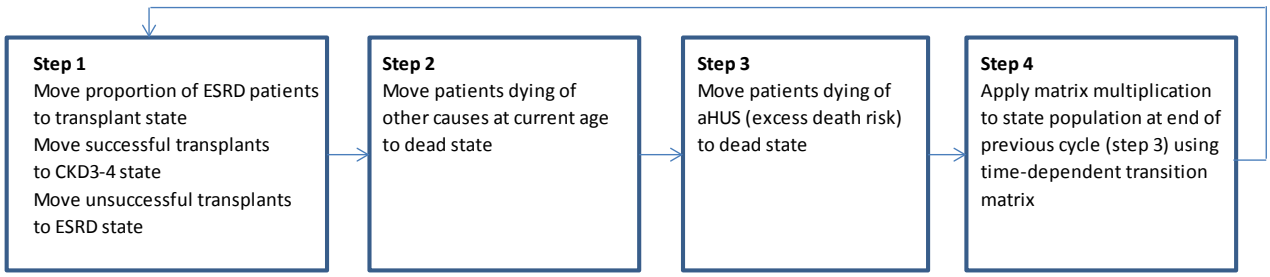
4. Transition probabilities are estimated and applied based on groups of CKD states (CKD0-2, CKD3-4, ESRD) rather than individual CKD states. This amendment was required to avoid the over-specification of the standard care transition probabilities (although this is essentially the same as how the manufacturer's model is structured).
5. Other cause mortality is applied using age-specific annual probabilities, adjusted down to 6-month transition probabilities, rather than using probabilities for particular age-bands. This amendment is minor and simply increases the accuracy of the other-cause mortality parameters.
6. Costs and health outcomes are discounted at 3.5%; this is in line with NICE's Reference Case for technology appraisals.

A brief manual describing how to amend the model's input parameters is provided in Appendix 2.

6.3.2 Changes to the model structure

The approach used to estimate health state populations is shown diagrammatically in Figure 7. The model begins with the initial state population, based on the pooled data from studies C08-002A/B and C08-003A/B,[1] defined in terms of states CKD0-2, CKD3-4 and ESRD. During the first step, this population is adjusted by (i) moving a proportion of ESRD patients to the transplant state, (ii) moving patients in whom transplantation has been successful from the transplant state to CKD3-4 and (iii) moving patients in whom transplantation has been unsuccessful from the transplant state back to the ESRD state. This adjusted state population forms the population for Step 2. During Step 2, patients who die of other causes are moved to the dead state. This adjusted state population forms the population for Step 3. During Step 3, patients who die of aHUS-related causes are transited to the dead state. This adjusted state population then forms the population for Step 4. During Step 4, simple matrix multiplication is applied to the adjusted state population using time-variant transition matrices. This adjusted state population then forms the population for Step 1. This adjustment cycle then repeats until the time horizon has been reached.

Figure 7: Iterative approach used to estimate health state populations conditional on competing events



6.3.3 Parameter values used in the ERG model

Table 36 shows all parameter values implemented in the ERG model, except for CKD transition probabilities. With the exceptions noted above, these are exactly the same as those used in the manufacturer's model, irrespective of whether the ERG believes them to be appropriate. Owing to time and resource constraints for this appraisal, the ERG model was developed deterministically and does not include uncertainty surrounding the model parameters.

Table 36: List of parameter values used in the ERG model (excluding CKD transition probabilities)

Parameter	Value	Source
General		
Discount rate - health outcomes	0.035*	NICE Methods Guide[86]
Discount rate –costs	0.035*	NICE Methods Guide[86]
Population parameters		
Patient start age	28	C08-002/C08-003[1]
Probability patient is female	0.65	C08-002/C08-003[1]
Other transition parameters		
Probability transplant | ESRD – eculizumab	0.00	MS assumption
Probability transplant | ESRD - standard care	0.04*	Noris *et al* (fitted)[11]
Probability transplant success	0.25	Legendre *et al*[39]
Probability excess death - SC first 6-month cycle	0.08*	Noris *et al* (fitted)[11]
Probability excess death - SC subsequent cycles	0.01*	Noris *et al* (fitted)[11]
Probability excess death aHUS - SC post-transplant	0.05	UK Renal Registry 15th Annual Report[77]
Health utilities		
HRQoL eculizumab CKD0-2	1.00	Manufacturer's assumptions based on studies C08-002A/B and C08-003A/B[1]
HRQoL eculizumab CKD3-4	0.87	
HRQoL eculizumab CKD5/ESRD	0.87	
HRQoL eculizumab transplant	0.66	
HRQoL standard care state utility loss	0.21	
HRQoL standard care CKD0-2	0.79	
HRQoL standard care CKD3-4	0.66	
HRQoL standard care CKD5/ESRD	0.66	
HRQoL standard care transplant	0.66	
Resource costs		
CKD0-2 (annual)	£960.00	Black *et al*[79]
CKD3-4 (annual)	£971.00	
CKD5/ESRD (annual)	£24,282.00	Black *et al*[79] and NHS Reference Costs 2011/12[80]
Transplant cost (one-off)	£18,792.00	NHS Reference Costs 2011/12[80]
Successful transplant maintenance (annual)	£6,641.00	NICE TA85[85]
Plasmapheresis (annual)	£31,148	NHS Reference Costs 2011/12[80]
Cost per dose eculizumab (300mg)	£3,150.00	BNF[25]
% administration covered by Alexion Homecare service	0.80	manufacturer's submission/model[1]
Cost eculizumab administration	£197.00	NHS Reference Costs 2011/12[80]
Meningococcal vaccine (once-only)	£30.00	BNF[25]
First 6-month eculizumab cost (including induction)	£177,454.40*	BNF[25]
Subsequent 6-month eculizumab cost (maintenance)	£164,824.40*	BNF[25]

**Different to manufacturer's model*

6.3.3.1 CKD transition probabilities – eculizumab group

The ERG has several concerns regarding the calculation of transition probabilities in the eculizumab group within the manufacturer's model. Separate data are available for 6-month intervals up to 42 months and the manufacturer's model calculates time-dependent CKD transition matrices using these data. However, in the manufacturer's analysis, these time-dependent matrices are then made time-invariant by weighting all matrices according to the number of observations at each time point. Whilst this approach uses all of the available data, the ERG believes this approach to be mathematically inappropriate as it fails to reflect the time-dependent nature of the observed data. In order to better reflect the available evidence relating to the effect of eculizumab on chronic kidney damage, the ERG calculated transition probabilities for each 6-month interval. Table 37 presents the time-dependent transition matrices together with the number of evaluable patients from whom these estimates are drawn. It should be noted that whilst full matrices could be calculated for the first six model cycles, there is noticeable attrition by 24-months, hence the model uses time-specific matrices for the first *four* cycles, then subsequently assumes that the matrix for 18-24 months applies indefinitely for all subsequent cycles. This extrapolation assumption is tested in the sensitivity analysis (see Table 41).

Table 37: Time-dependent transition probabilities calculated using patient-level data from studies C08-002A/B and C08-003A/B

Transition probabilities				Number of evaluable patients
Baseline to 6 months (applied in cycle 1 in ERG model)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
6 months to 12 months (applied in cycle 2 in ERG model)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
12 months to 18 months (applied in cycle 3 in ERG model)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
18 months to 24 months (applied in cycle 4 and subsequently in ERG model)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
24 months to 30 months (not used in ERG base case)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
30 months to 36 months (not used in ERG base case)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]	[redacted]	[redacted]	
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	
30 months to 42 months (not used in ERG model)				
	CKD0-2	CKD3,4	CKD5	[redacted]
CKD0-2	[redacted]			
CKD3,4	[redacted]	[redacted]	[redacted]	
CKD5	[redacted]	[redacted]	[redacted]	

Figure 8 presents the Markov trace for the first three years of the ERG model compared against the observed CKD state data from studies C08-002A/B and C08-003A/B. A comparison of Figure 8 and Figure 6 clearly indicates that the ERG model provides a closer fit to the observed data than the manufacturer's model. Given the method for estimating transition probabilities in the ERG model, the only source of error between predicted and observed CKD state membership arises from the presence of censored observations at each timepoint.

Figure 8: Comparison of observed and predicted CKD state during the first two years of eculizumab treatment

[redacted]

[redacted]

6.3.3.2 CKD transition probabilities – standard care group

The ERG has serious concerns regarding the calculation of the CKD transitions for the standard care group, as detailed in Section 5.5. In order to address these problems, the ERG model was fitted to observed data relating to the probability of ESRD and death (i) following the initial aHUS episode, and (ii) at 3-years from an analysis of registry data reported by Noris *et al*.[11] In this registry, 273 consecutive patients were recruited and followed up for up to 10 years. A summary of these data are presented in Tables 14 and 38. Following the initial aHUS episode, 36% patients were in ESRD and 8% patients had died. At 3-years following entry into the registry, 45% patients were in ESRD and 11% patients had died. Noris *et al*[11] also report data on the number of transplants over the observed period (n=64); the distribution of transplants at each timepoint is not calculable from the publication. It should be noted that the ERG did not have access to information on the initial distribution of patients by CKD state upon entry into the registry. However, Professor Noris, Principal Investigator of the registry, informed the ERG that the proportion of patients in ESRD was approximately 0.44 (*Personal communication: Professor Marina Noris, Clinical Research Center for Rare Diseases "Aldo e Cele Daccò", Italy).* Within the fitting process, we assumed that the initial CKD distribution reflects that observed in studies C08-002A/B and C08-003A/B; this may bias against standard care.

Table 38: Summary of patients reaching ESRD or death in Noris *et al* registry[11]

	Abnormality	CFH	CFI	C3	THBD	MCP	CFH antibodies	None	All patients
Initial aHUS episode	N	62	10	12	13	17	8	128	250
	ESRD	0.31	0.6	0.58	0.46	0.06	0.37	0.37	0.36
	Death	0.19	-	-	0.31	-	-	0.04	0.08
3 years	N	64	10	12	13	17	8	119	243
	ESRD	0.53	0.6	0.67	0.23	0.06	0.63	0.43	0.45
	Death	0.23	-	-	0.31	-	-	0.07	0.11

In order to better reflect the apparent time-dependent nature of the estimates reported by Noris *et al*,[11] the ERG model includes two transition matrices. The first matrix of transition probabilities is applied only for the first cycle and is assumed to reflect the timepoint of the initial aHUS episode (the mean timepoint of the first aHUS episode is not reported by Noris *et al*[11]). The second matrix is applied indefinitely for all subsequent cycles. We set up a simple Solver routine using the mean squared error (MSE) between the model and the data to fit the following model transition probabilities:

- 6 month transition probability from CKD0-2 to CKD3-4 (first cycle)
- 6 month transition probability from CKD3-4 to ESRD (first cycle)
- 6 month transition probability from CKD0-2 to CKD3-4 (subsequent cycles)
- 6 month transition probability from CKD3-4 to ESRD (subsequent cycles)
- 6 month transition probability of undergoing transplant conditional on the patient being in ESRD
- aHUS excess death probability for all CKD states (first cycle)
- aHUS excess death probability for all CKD states (subsequent cycle).

No constraints were set within the Solver fitting routine except that all probability values were bounded by 0 and 1. All other transitions for the standard care group (e.g. the probability that transplantation is successful) reflect the values used in the manufacturer's model. The model uses initial values of 0.50 for all fitted parameters.

Table 39 shows the model fit compared against the observed data reported by Noris *et al*. It can be seen that the MSE is very small, hence the ERG model fits the observed data very closely. This is not surprising as this approach involves fitting seven unknown parameters to five observed data points. In other words, it is highly likely that the model has been over-fitted; this is unfortunately unavoidable given the limited data reported in the Noris publication. The stability of the model fitting process is examined in Section 6.4.3. For information, the table also shows the manufacturer's estimate of the proportion of patients in ESRD and death at each timepoint. It can be seen that the manufacturer's model produces broadly similar estimates of ESRD at each timepoint, however the probability of death is markedly higher than that observed within Noris *et al*.[11]

Table 39: Observed versus predicted events from Noris *et al*[11]

Timepoint	Event	Data	ERG model	MSE	Manufacturer's model
Initial episode	ESRD	0.36	0.36	0.000000	0.39
	Dead	0.08	0.08	0.000000	0.04
3 years	ESRD	0.45	0.45	0.000000	0.51
	Dead	0.11	0.11	0.000000	0.25
	Transplant	0.10	0.10	0.000000	0.13
-	Sum	-	-	0.000000	-

Table 40 presents the standard care CKD transition probabilities estimated by fitting the model to data reported by Noris *et al*.[11]

Table 40: Transition probabilities calculated by fitting the model to observed events reported by Noris *et al*[11]

Transition probabilities				Number of patients in registry at timepoint
Baseline to 6 months				
	CKD0-2	CKD3,4	CKD5	250
CKD0-2	0.51	0.49	0.00	
CKD3,4	0.00	0.86	0.14	
CKD5	0.00	0.00	1.00	
6 months to 12 months and all subsequent 6-month cycles				
	CKD0-2	CKD3,4	CKD5	243
CKD0-2	0.52	0.48	0.00	
CKD3,4	0.00	0.95	0.05	
CKD5	0.00	0.00	1.00	

6.3.4 Summary of additional analyses undertaken using the ERG model

The following analyses were undertaken using the ERG's exploratory model:

- Base case analysis (costs and outcomes discounted at 3.5%)
- Costs and outcomes undiscounted
- Costs and outcomes discounted at 1.5%
- Same utilities for eculizumab and standard care based on eculizumab values
- Same utilities for eculizumab and standard care based on standard care values
- Future eculizumab transition probabilities based on matrix derived from interval 12 months to 18 months
- Future eculizumab transition probabilities based on matrix derived from interval 30 months to 36 months

- Future eculizumab transition probabilities based on matrix derived from interval 36 months to 42 months
- Standard care probabilities fitted to data on ESRD and death reported by Fremeaux-Bacchi *et al*[32] (death = 0.8% at 1-year and 0.8% at 5-years; ESRD = 55% at 1-year and 63% at 5-years).
- Standard care probabilities fitted to data on ESRD and death reported by Fremeaux-Bacchi *et al*[32] (death = 0.8% at 1-year and 0.8% at 5-years; ESRD = 55% at 1-year and 63% at 5-years) plus same utilities for eculizumab and standard care based on eculizumab values
- Standard care probabilities fitted to data on ESRD and death reported by Fremeaux-Bacchi *et al*[32] (death = 0.8% at 1-year and 0.8% at 5-years; ESRD = 55% at 1-year and 63% at 5-years) plus same utilities for eculizumab and standard care based on standard care values

6.4 Cost-consequence results produced using the ERG model

6.4.1 Headline cost-consequence results produced using the ERG model

Table 41 presents the headline cost-consequence results of the ERG model. As noted above, these do not reflect uncertainty in model parameters and thus do not capture any potential non-linearity between the model inputs and outputs.

Table 41: Headline cost-consequence results produced using the ERG model (discounted at 3.5%)

Outcome	Eculizumab	Standard care	Incremental
Undiscounted results			
Life years gained	53.80	35.47	18.33
QALYs gained	48.97	23.40	25.57
Total costs	[redacted]	£951,600	[redacted]
Health outcomes and costs discounted at 3.5%			
Life years gained	23.99	17.71	6.28
QALYs gained	21.83	11.69	10.14
Total costs	[redacted]	£305,672	[redacted]

Without discounting, the model estimates a mean survival of 53.80 years for patients receiving eculizumab and a mean survival of 35.47 years for patients receiving standard care; the incremental survival gain for eculizumab versus standard care is estimated to be 18.33 undiscounted life years gained. The model suggests that patients receiving eculizumab will gain 48.97 QALYs whilst patients in the standard care group will gain 23.40 QALYs; this gives an undiscounted difference of 25.57 additional QALYs for the eculizumab group. The estimated cost per patient within the eculizumab group is [redacted] compared against [redacted] in the standard care group.

Given a discount rate of 3.5% for costs and health outcomes, the model suggests that eculizumab is expected to produce 10.14 additional QALYs compared against standard care at an additional discounted cost of [redacted].

These results indicate a substantial difference between the manufacturer's model and the ERG model. In particular, the estimates of overall survival for the standard care group is substantially higher in the ERG model (ERG model=35.47 undiscounted life years, manufacturer's model=9.97 undiscounted life years), although it is also noteworthy that the manufacturer's model likely underestimates overall survival in the eculizumab group due to the inappropriate method of handling other-cause mortality (ERG model=53.80 undiscounted life years, manufacturer's model=47.62 undiscounted life years). These differences in survival, together with different sojourn times in CKD states and lower transplant rates for standard care patients, lead to comparatively lower estimates of incremental QALYs gained between the groups within the ERG model. In addition, the ERG estimate of the incremental cost of eculizumab versus standard care is higher than that presented by the manufacturer (ERG model [discounted at 3.5%]=[redacted], manufacturer's model [discounted at 3.5%]=[redacted]).

6.4.2 Intermediate results produced by the ERG model

Figures 9 and 10 present a breakdown of undiscounted costs for the eculizumab and standard care groups respectively. It is evident from these figures that the vast bulk of total cost between the two groups is attributable to the acquisition cost of eculizumab ([redacted] per patient).

Figure 9: Cost breakdown for eculizumab group (undiscounted)

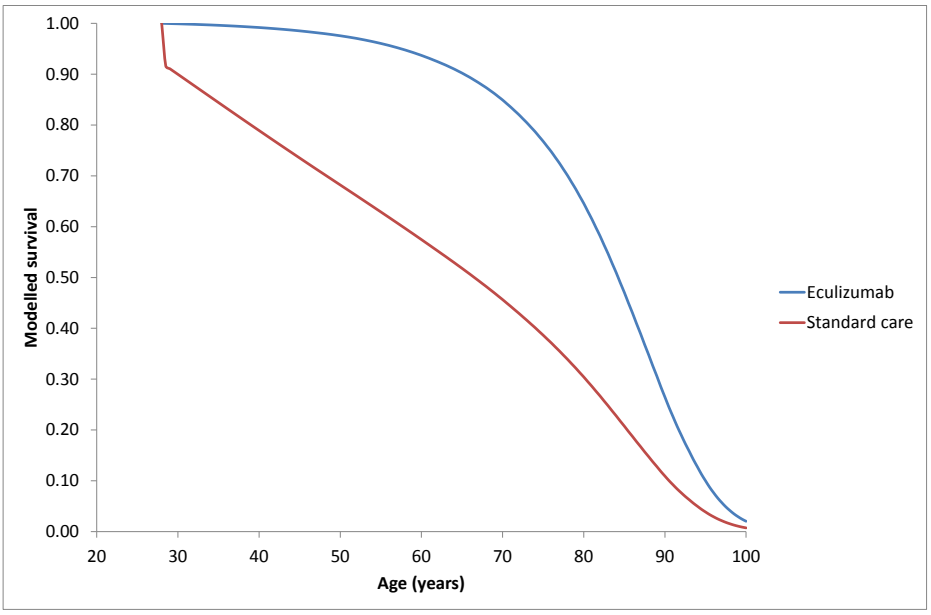
[redacted]

Figure 10: Cost breakdown for standard care group (undiscounted)

[redacted]

Figure 11 presents projected overall survival curves from the ERG model (note the curve starts at age 28 years – the age of the cohort at entry into the model). Unsurprisingly, given the manufacturer's potentially optimistic assumptions regarding the elimination of the risk of aHUS-related death (an assumption maintained within the ERG model), the overall survival curve for eculizumab broadly reflects that of a normal healthy population. Within the standard care group, the model predicts an immediate drop in survival (reflected in the transition matrix for the first aHUS episode) with a faster rate of death compared to eculizumab thereafter. This reflects the observed data reported by Noris *et al.*[11]

Figure 11: Modelled survival curves for patients receiving eculizumab and patients receiving standard care



Figures 12 and 13 present the Markov traces for the eculizumab group and the standard care groups respectively. The trace for the eculizumab group indicates that initially patients undergo rapid changes in health state, with the overall membership of all living health states remaining relatively stable over time. Conversely, within the standard care group, the proportion of patients in CKD0-2 remains low throughout, whilst the proportion of patients reaching ESRD increases considerably and becomes the predominant living health state within the first 15-years of the modelled time horizon. These traces are very different to those predicted using the manufacturer's model (see Figures 2 and 3).

Figure 12: Markov trace for eculizumab group

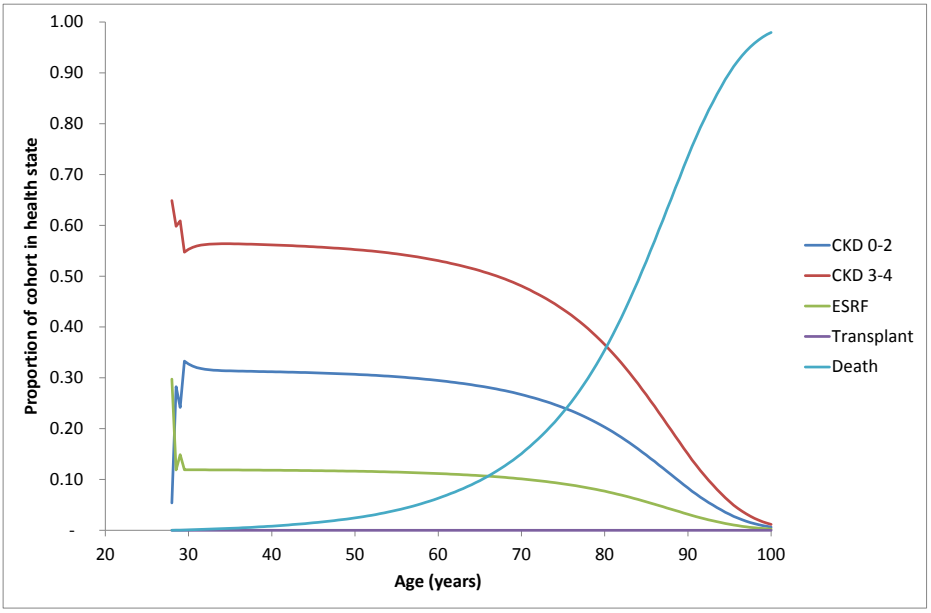
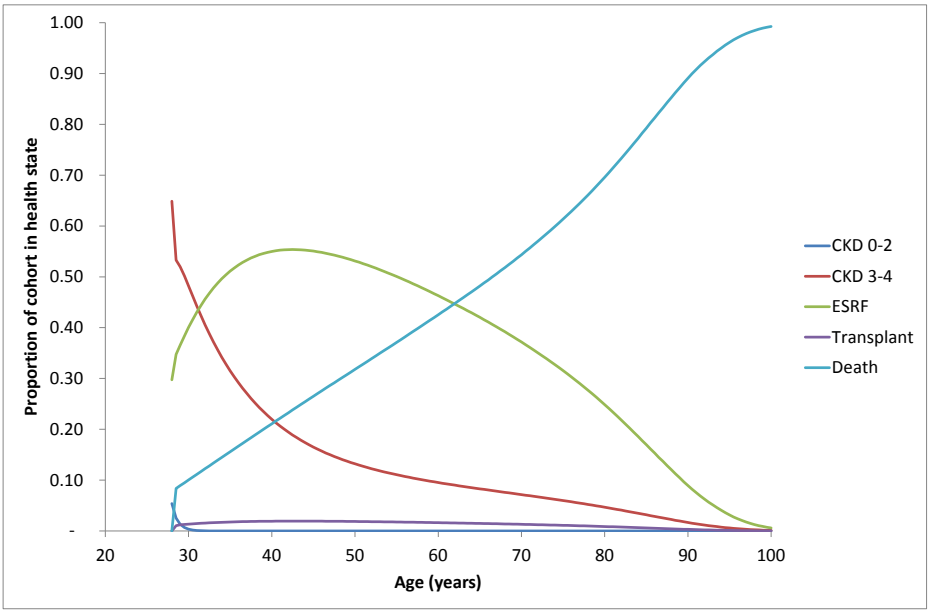


Figure 13: Markov trace for standard care group



6.4.2 Exploratory sensitivity analyses produced using the ERG model

Table 42 presents the results of the exploratory sensitivity analysis using the ERG model.

Table 42: Exploratory sensitivity analysis using the ERG model

Outcome	Eculizumab	Standard care	Incremental
Costs and outcomes discounted at 1.5%			
Life years gained	36.47	25.37	**11.10**
QALYs gained	33.19	16.74	**16.45**
Total costs	[redacted]	£520,627	[redacted]
Health utilities same for eculizumab and standard care (eculizumab values)			
Life years gained	23.99	17.71	**6.28**
QALYs gained	21.83	15.29	**6.54**
Total costs	[redacted]	£305,672	[redacted]
Health utilities same for eculizumab and standard care (standard care values)			
Life years gained	23.99	17.71	**6.28**
QALYs gained	16.84	11.69	**5.15**
Total costs	[redacted]	£305,672	[redacted]
Transition probabilities projected from matrix for interval 12 months to 18 months			
Life years gained	23.99	17.71	**6.28**
QALYs gained	23.58	11.69	**11.90**
Total costs	[redacted]	£305,672	[redacted]
Transition probabilities projected from matrix for interval 24 months to 30 months			
Life years gained	23.99	17.71	**6.28**
QALYs gained	21.85	11.69	**10.16**
Total costs	[redacted]	£305,672	[redacted]
Transition probabilities projected from matrix for interval 30 months to 36 months			
Life years gained	23.99	17.71	**6.28**
QALYs gained	21.05	11.69	**9.36**
Total costs	[redacted]	£305,672	[redacted]
Standard care probabilities fitted using Fremeaux-Bacchi et al[32]			
Life years gained	23.99	23.07	**0.92**
QALYs gained	21.83	15.23	**6.60**
Total costs	[redacted]	£367,758	[redacted]
Standard care probabilities fitted using Fremeaux-Bacchi et al[32] plus health utilities same for eculizumab and standard care (eculizumab values)			
Life years gained	23.99	23.07	**0.92**
QALYs gained	21.83	19.94	**1.89**
Total costs	[redacted]	£367,758	[redacted]
Standard care probabilities fitted using Fremeaux-Bacchi et al[32] plus health utilities same for eculizumab and standard care (standard care values)			
Life years gained	23.99	23.07	**0.92**
QALYs gained	16.84	15.23	**1.61**
Total costs	[redacted]	£367,758	[redacted]

The results presented in Table 42 indicate that the assumption of differential HRQoL for the same CKD state has a substantial impact upon the incremental QALYs gained for eculizumab versus standard care. Across these exploratory scenarios, the incremental health gain for eculizumab versus standard care range from 1.61 to 16.45 QALYs gained. The incremental cost for eculizumab versus standard care is similar across all scenarios except where the discount rate is changed. The analysis

indicates that the manufacturer's assumption of differential HRQoL produces a very favourable result for eculizumab. In addition, the exploratory sensitivity analysis suggests that the incremental QALY estimates are sensitive to which 6-month transition matrix is used to extrapolate future CKD damage.

6.4.3 Examination of stability of standard care transition probabilities

As noted in Section 6.3.3.2, the standard care group is likely to have been over-fitted due to the limitations of the data reported in the paper by Noris *et al.*[11] We undertook further analyses to examine the potential impact of this by using different initial values within the fitting routine. Initial values for all fitted parameters were set to 0, 0.25, 0.50, 0.75 and 1.0. Table 43 shows the results of these analyses.

The results presented in Table 43 show that the initial values selected do have an impact upon the model fitting results. For higher initial values, the model does not fit the registry data well (MSE=0.9877) hence the results using these values cannot be considered to be reliable. For lower initial values (0 to 0.5), the model provides a very good fit and the estimates of incremental costs and incremental QALYs gained remain stable.

Table 43: ERG results given different initial values of standard care transition probabilities

Outcome	Eculizumab	Standard care	Incremental
All initial values set to 0 (MSE=0.0000)			
Life years gained	23.99	17.72	**6.27**
QALYs gained	21.83	11.82	**10.01**
Total costs	[redacted]	£306,736	[redacted]
All initial values set to 0.25 (MSE=0.0000)			
Life years gained	23.99	17.70	**6.29**
QALYs gained	21.83	11.69	**10.14**
Total costs	[redacted]	£305,449	[redacted]
All initial values set to 0.50 (MSE=0.0000)			
Life years gained	23.99	17.71	**6.28**
QALYs gained	21.83	11.69	**10.14**
Total costs	[redacted]	£305,672	[redacted]
All initial values set to 0.75 (MSE=0.9877)			
Life years gained	23.99	0.72	**23.27**
QALYs gained	21.83	0.48	**21.35**
Total costs	[redacted]	£21,878	[redacted]
All initial values set to 1.00 (MSE=0.9877)			
Life years gained	23.99	0.72	**23.27**
QALYs gained	21.83	0.48	**21.35**
Total costs	[redacted]	£21,878	[redacted]

6.5 Discussion

This chapter has presented the methods and results of an exploratory ERG model which resolves the mathematical errors and irregularities identified in the manufacturer's model, yet, as far as possible, retains the structure and assumptions employed by the manufacturer. The main difference between the ERG model and the manufacturer's model reflects the use of registry data to characterise prognosis in patients receiving standard care, rather than the use of short-term pre-treatment phase data from studies C08-002A/B and C08-003A/B (see Section 5.5, point 2a). The ERG model suggests a substantially lower incremental QALY gain compared to that estimated by the manufacturer. This difference is driven principally by the very poor prognosis indicated by the manufacturer's model analysis, which applies a 4% risk of aHUS death every 6-months,[1] as compared against the considerably less poor mortality rate indicated in the aHUS registries, whereby the initial risk of death is high but reduces considerably thereafter. The estimated incremental cost of eculizumab versus standard care is also higher in the ERG model; this likely to be largely driven by the exclusion of paediatric dose reductions.

The ERG believes that the model presented in this chapter is more suitable for decision-making than the analysis presented by the manufacturer. However, there remain a number of limitations. Firstly, the number of datapoints within the registry publications to fit the standard care transition parameters is limited; the consequence of this is that the model is likely to be over-fitted hence multiple combinations of parameter values may provide a suitable fit to the data. The ERG contacted Professor Noris, the principal investigator of the Italian aHUS registry, to request further data on CKD distributions at baseline, following the initial aHUS episode and at 3-years. However, these data were not available prior to the completion of this report. The ERG also note that the method used to fit the data do not adequately reflect the uncertainty in the parameters. It would be preferable to use more sophisticated calibration methods, such as Markov Chain Monte Carlo (MCMC) approaches to produce samples from the posterior distribution of the correlated parameters. The ERG also note that the two aHUS-specific registries considered within this economic analysis have not been identified through a detailed systematic review, hence other potentially relevant data may exist elsewhere. The long-term prognosis of patients with aHUS, with eculizumab treatment or without, remains an area of considerable uncertainty.

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

Alongside the cost-consequence model used to examine the extent to which eculizumab offers value for money for the NHS, the MS[1] also includes details of a budget impact model. The two models are related. The cost-consequence model estimates total costs and QALYs over a lifetime horizon for a hypothetical cohort of aHUS patients. The budget impact model estimates the total costs to the NHS for the period beginning of 2013 to the end of 2017.

This budget impact model draws on intermediate estimates of cost and health state membership from the cost-consequence model (see Chapter 5). The model defines two scenarios: (1) a scenario in which a proportion of patients receive eculizumab with the remainder receiving standard care, and (2) a scenario in which all patients receive standard care. The net budget impact for the NHS is calculated as the difference between these two scenarios.

The manufacturer's budget impact model estimates the total number of diagnosed aHUS patients given a starting population for England of 52.6million, a growth rate of 1.008, a prevalence of 5.5 persons per million and an incidence rate of 0.60 persons per million.[1] The model predicts a total eligible population of [redacted] patients in 2013, rising to [redacted] patients in 2017. For the scenario in which eculizumab is available, the model assumes a staggered increase in uptake of the technology over time (see Table 44); the MS states that these estimates are based on Alexion's recent experience in PNH and their experience to date with aHUS (MS page 181).

Table 44: Assumed uptake of eculizumab in England during the period 2013-2017

Time	Percent patients receiving eculizumab	Percent patients receiving standard care
Year 1 (2013)	[redacted]	[redacted]
Year 2 (2014)	[redacted]	[redacted]
Year 3 (2015)	[redacted]	[redacted]
Year 4 (2016)	[redacted]	[redacted]
Year 5 (2017)	[redacted]	[redacted]

The model includes estimated costs per incident and prevalent patient separately for eculizumab-treated patients using the Markov trace for the first 5-years of the cost-consequence model and the costs of eculizumab and CKD management. This includes reduced costs of eculizumab associated with dose adjustments for paediatric patients ([redacted] of the assumed population). Administration costs do not appear to have been included in the analysis. The death rate due to aHUS or other causes during the period 2013-2017 is assumed to be zero. For patients receiving standard care, the Markov trace for the first 5-years of the cost-consequence model is used together with the associated costs of

CKD management and plasmapheresis to produce a mean cost per year of treatment. Plasmapheresis is costed only using the unit cost estimate for adults and does not include the paediatric cost applied in the cost-consequence model. A mortality rate of 8% is applied to patients receiving standard care each year.

Table 45 presents the headline budget impact analysis results based on the assumptions employed by the manufacturer (note this has been re-labelled by the ERG to aid interpretation).

Table 45: Headline budget impact analysis results presented by the manufacturer

	Year 1 (2013)	**Year 2 (2014)**	**Year 3 (2015)**	**Year 4 (2016)**	**Year 5 (2017)**	**Total over period**
Scenario in which eculizumab is available (a proportion receive standard care)						
Eculizumab costs (A)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other direct medical costs (B)	£194,571	£405,336	£638,437	£750,363	£872,424	£2,861,130
Standard care costs (C)	£5,460,838	£4,684,307	£3,864,755	£3,716,426	£3,535,340	£21,261,665
Total (A+B+C)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario in which eculizumab is not available (all receive standard care)						
Standard care costs (D)	£6,424,516	£6,614,841	£6,795,528	£6,967,395	£7,131,198	£33,933,477
Net budget impact (A+B+C-D)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The analysis presented by the manufacturer suggests that without eculizumab, the absolute cost of treating patients with aHUS is between £6.4million and £7.1million each year. Based on the manufacturer's analysis, the net budget impact of recommending eculizumab will be approximately [redacted] in 2013, rising to [redacted] in 2017. The overall 5-year predicted net budget impact will be around [redacted] over the period 2013-2017.

7.2 ERG critique of the manufacturer's budget impact analysis

The ERG notes the following key points with respect to the manufacturer's budget impact analysis:

- These estimates are based on optimistic assumptions about detecting patients with early disease and may not reflect the current distribution of disease severity in England.
- The analysis does not include estimates of PSS costs; this is inconsistent with the manufacturer's estimates of wider societal benefits (see Chapter 8) as carer costs are likely to be relevant for a proportion of aHUS patients.

- The estimates of uptake appear very low and are likely to reflect a situation in which eculizumab has not been granted a positive recommendation for coverage/reimbursement. The ERG believes that a positive NICE recommendation would lead to considerably higher rates of uptake and that the manufacturer's analysis therefore underestimates the anticipated NHS budget impact resulting from the introduction of this technology.
- The costs of administration do not appear to be included in the costs of treating a patient with eculizumab. This will lead to an underestimation of the net budget impact.
- The budget impact model seems inconsistent in that paediatric dose reductions are included for eculizumab but not for plasmapheresis. This inconsistency may serve to dilute the incremental cost of eculizumab.
- Some patients receiving eculizumab will likely die during the projected 5-year period considered within the analysis. This is not reflected in the budget impact model; its inclusion would reduce the net budget impact estimates.

In light of these concerns, the ERG presents an additional analysis in which varying levels of uptake are assumed (see Table 46). For brevity, only the net NHS budget impact is presented for each scenario.

Table 46: Budget impact assuming varying levels of uptake of eculizumab

Scenario	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)	Total over period
Manufacturer's estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake=100%/yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake=80%/yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake=60%/yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake=40%/yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake=20%/yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This analysis indicates that given an uptake of 100%, the net NHS budget impact associated with the introduction of eculizumab would be substantially higher than the estimates presented by the manufacturer. Assuming 100% uptake, the budget impact model predicts a 5-year net budget impact of in excess of [redacted] over the period 2013 to 2017.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the MS

8.1.1 Nature of estimates presented

The MS includes estimates of impacts of eculizumab on (i) lost productivity, government benefits and tax revenues for patients and current/ex carers of aHUS patients, (ii) estimates of cost-savings associated with out-of-pocket expenditures for patients and carers including, transportation, housing and other costs; and (iii) other carer costs (see MS[1] pages 189-201).[1] These estimates have been produced using a large number of disparate sources. The three groups of wider societal benefits are summarised in turn, based on information presented in the MS, and accompanied by a brief commentary on each from the ERG. It should be noted that the MS implies that these cost-savings would accrue annually (see MS[1] pages 18, 191, 194 and 198).

Each group of estimated cost-savings is presented across three scenarios based on the potential effectiveness of eculizumab (full effectiveness for 289 patients, 75% effectiveness and 25% effectiveness). Whilst not clear from the MS, the ERG assumes that lower levels of effectiveness are intended to relate to the percentage of patients receiving eculizumab (with complete cure for each individual patient) rather than the percentage of patients in whom eculizumab is clinically effective. None of the three scenarios however reflect the levels of uptake assumed within the NHS budget impact analysis presented in Chapter 7 ([redacted] rising to [redacted] over 5 years).

8.1.2 Societal costs

Table 47 presents a summary of estimated non-health cost-savings presented by the manufacturer.

Lost productivity for patients was estimated by comparing the proportion of adult aHUS patients who were unemployed (not retired) in the UK aHUS patient survey[1] with the current UK unemployment rate (assumed to be 20%). The monetary value of this difference in employment status was valued assuming a median salary of £26,500.[92] Lost productivity for carers was estimated in a similar manner using findings from the UK aHUS patient survey which suggested that 54% of patients had an informal carer and that carers lost an average of 18 hours of paid work a week due to their carer responsibilities.

Government disability-related benefit payments were estimated by assuming that 25% of aHUS patients would be in receipt of benefits, with a monetary value of £235 per week (based on Wood *et al*, full reference not included in MS[1]). The manufacturer also assumed that 61% of carers receive a

carer's allowance of £59.75 per week (based on "Carers UK, 2007", full reference not included in MS[1]).

Lost tax revenues associated with aHUS were estimated based upon the estimates of lost productivity for patients and carers assuming that the mean percentage of salaries paid to the government in tax is 17.8%.[93]

Table 47: Estimated societal cost savings presented by the manufacturer

Manufacturer's description of cost component	**Scenario 1: Cost savings assuming 100% effective**	**Scenario 2: Cost savings assuming 75% effective**	**Scenario 3: Cost savings assuming 25% effective**
Patient lost productivity	£784,400	£588,300	£196,100
Carer lost productivity (current carers)	£1,597,729	£1,198,297	£399,432
Carer lost productivity (ex-carers)	£804,010	£603,008	£201,003
Patient receipt of government benefits	£904,280	£678,210	£226,070
Carer receipt of government benefits	£248,411	£186,308	£62,102
Lost tax revenues for patients	£279,246	£209,434	£69,812
Lost tax revenues for carers	£284,396	£213,297	£71,098

The ERG has not undertaken a detailed critique of these analyses, but notes the following issues:

- These estimates relate to a current assumed cohort of 289 aHUS patients and do not account for rising rates of aHUS diagnosis over time.
- The analysis considers non-NHS cost-savings for eculizumab versus standard care *given that an aHUS patient is still alive*. The appropriate societal valuation of production over consumption should take account of differential survival between the treatment options.
- Receipt of government benefits and lost tax revenues should not be included in the analysis as they are transfer payments (payments whereby a transfer is made without any exchange of goods or services). Transfer payments may change the distribution of income or wealth, but do not give rise to economic costs,[94] and should not be included in a societal analysis. The inclusion of these items will result in a substantial overestimate of the potential non-health cost-savings.
- The estimates appear to assume that all aHUS patients will no longer lose productivity after starting treatment with eculizumab. This appears to implicitly assume that all patients will effectively be cured by the treatment.

- Lost productivity appears to have been calculated assuming a human-capital approach. This method can produce considerably higher estimates of lost productivity compared to friction costing approaches.[95]
- It is unclear why ex-carers should be included in any analysis of productivity losses. Their inclusion seems to assume that these individuals, if out of work, will be unemployed indefinitely. This is unlikely to be a reasonable assumption and will overestimate projected cost-savings.
- No consideration is given to the impact on lost productivity of other diseases and conditions which may impact upon the future health of aHUS patients. In other words, the analysis appears to assume that (a) every aHUS patient will be cured and (b) after starting eculizumab treatment they will never lose productivity due to other unrelated diseases they develop in the future.
- The MS indicates that these cost-savings are accrued annually hence costs saved in future years should be discounted.
- Estimates are presented as absolute costs rather than net cost savings. No consideration is given to the potential productivity loss savings associated with the displacement of other technologies in order to fund eculizumab.

8.1.3 Costs borne by patients

The MS includes estimates of out-of-pocket expenses incurred by aHUS patients. Table 48 presents a summary of the estimated out-of-pocket cost savings borne by patients as presented by the manufacturer; it should be noted that there appears to be a presentation error in the manufacturer's table hence the estimates for accommodation and direct financial expenditures have been imputed by the ERG.[1] Again, this analysis is presented across three scenarios based on the potential effectiveness of eculizumab.

Transport costs were estimated based on the assumption that aHUS patients spend four hours travelling each week for activities associated with their aHUS (e.g. hospital visits).[1] A mean cost of £7.50 per trip is assumed. The MS notes uncertainty surrounding this cost.

Household expenses were assumed to relate to adaptations required for home dialysis. The manufacturer assumes that 31% of aHUS patients are on home dialysis. The cost of home conversion was assumed to be £1,291 annually over four years.[96]

Accommodation costs were estimated to reflect the circumstance in which a patient moves into a carer's home. The MS attempts to value this in terms of the opportunity cost of earning a market rent, which is estimated to be £4,834 per year based on the assumption that 10% of informal carers take in aHUS patients. No further details are presented to support these values.

Costs associated with moving house were included to reflect the situation in which patients had to move home as a result of their (or their child's) aHUS. The average cost associated with moving home in the UK was assumed to be £8,922.[97]

Table 48: Estimated out-of-pocket cost savings presented by the manufacturer

Manufacturer's description of cost component	Scenario 1: Cost savings assuming 100% effective	Scenario 2: Cost savings assuming 75% effective	Scenario 3: Cost savings assuming 25% effective
Transport	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.	£40,277	£30,208	£10,069
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.	£63,359	£47,518	£15,840
Requirement to move house, e.g. due to mains water supply needed for haemodialysis	£581,048	£435,786	£145,262

The ERG has not undertaken a detailed critique of these analyses, but notes the following issues:

- These estimates relate to a current assumed cohort of 289 aHUS patients and do not account for rising rates of aHUS diagnosis over time.
- The transport costs appear to assume that no aHUS patients will be required to attend hospital after starting eculizumab. Given the nature of the disease, this is unrealistic.
- Costs associated with home adaptation and moving house are likely to be incurred only once; assuming that these would recur each year would likely substantially overestimate savings in out-of-pocket expenses.
- The MS indicates that these cost-savings are accrued annually hence costs saved in future years should be discounted.
- Estimates are presented as absolute costs rather than net cost savings. No consideration is given to the potential out-of-pocket costs associated with the displacement of other technologies in order to fund eculizumab.

8.1.4 Other carer costs

The MS also includes estimates of other carer costs, defined in terms of the value of informal care, healthcare service use by carers and social care opportunity costs. These estimates are summarised in

Table 49. Again, there appears to be a formatting error in the MS, hence the ERG have imputed some of the values in Table 49.

The cost of informal care was estimated to be £33,176 per year (based on "NHS Information Centre", full reference not included in MS[1]); this was assumed to apply to 44% of aHUS patients.

Costs associated with healthcare use by carers were assumed to cost £475 per carer, based on a study of the effectiveness and cost-effectiveness of support and services to informal carers of older people.[98]

The average cost to the carer was estimated in 1990 to be £31.42 a week.[99] This cost is reported to include direct financial expenditure on goods and services, forgone non-waged time, forgone waged time, forgone career prospects, and forgone accommodation costs.

Table 49: Estimated other carer cost savings presented by the manufacturer

Manufacturer's description of cost component	**Scenario 1: Cost savings assuming 100% effective**	**Scenario 2: Cost savings assuming 75% effective**	**Scenario 3: Cost savings assuming 25% effective**
Value of informal care provided by carers	£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	£62,214	£46,660	£15,553.50
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.	£160,609	£53,536	£40,152.25

The ERG has not undertaken a detailed critique of these analyses, but notes the following issues:

- These estimates relate to a current assumed cohort of 289 aHUS patients and do not account for rising rates of aHUS diagnosis over time.
- It is unclear whether carer health care resource use would be impacted at all by the introduction of eculizumab (presumably carers would still need to see their GP, dentist etc.) irrespective of whether eculizumab is available or not.
- The source for social opportunity cost is old and may not reflect current values.

- The MS indicates that these cost-savings are accrued annually hence costs saved in future years should be discounted.
- Estimates are presented as absolute costs rather than net cost-savings. No consideration is given to the potential carer costs associated with the displacement of other technologies in order to fund eculizumab.

8.1.5 Discussion of wider societal (non-health) benefits

The ERG would suggest that the projected cost-savings presented by the manufacturer can only be interpreted in the context of other non-health costs and cost-savings associated with other treatments that would be displaced by the introduction of eculizumab. No information relating to *net* cost savings is presented in the MS taking into account the non-health benefits likely to be forgone through the introduction of eculizumab; as a consequence, the ERG believe that the value of these estimates for decision-making is limited.

8.2 Staffing and infrastructure requirements associated with the use of the technology

The MS states the following with respect to staffing and infrastructure requirements:

"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… Infrastructure requirements are limited to the additional resource requirements within centres 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."

Whilst the MS indicates that eculizumab is suitable for administration in centres by healthcare professionals, it is unclear how this will fit in with the manufacturer's proposed Homecare Initiative (note that the cost-consequence analysis detailed in Chapter 5 indicates that 80% of all eculizumab administration costs will be borne by the manufacturer). The overall resource requirements associated with the use of eculizumab are thus unclear to the ERG.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

The clinical evidence in the MS is based on a systematic review of eculizumab for the treatment of patients with aHUS. In the absence of RCT evidence, the systematic review identified and included two published (C08-002A/B, C08-003A/B) and two unpublished (interim data from C10-003 and C10-004) prospective studies and one retrospective study (C09-001r).

All prospective studies were manufacturer sponsored, phase 2, open label, non–randomised, single arm studies that included a diverse range of patients. Study C08-002A/B included aHUS patients (aged ≥12 years) resistant to plasma therapy (n=17), whereas study C08-003A/B included aHUS patients (aged ≥12 years) that were plasma therapy sensitive (n=20). The unpublished C10-003 study included children (aged between 1 month to 18 years) with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine (n=22). In this study, patients could receive no more than five weeks of PE/PI prior to enrolment. In contrast, the C10-004 study included adult patients (aged over 18 years) with aHUS exhibiting thrombocytopenia, haemolysis and elevated serum creatinine (n=41). In this study there was no requirement for the patients to be undergoing plasma therapy. The retrospective observational study included 30 patients (paediatrics, adolescents, and adults) who had been diagnosed with aHUS who received at least one dose of eculizumab between 2007 and 2009 outside of a manufacturer sponsored study.[44]

The prospective efficacy data generally indicated that eculizumab was effective in a diverse range of patients with aHUS. Compared with baseline, improvements were observed in normalisation of platelet count, TMA activity, renal function and quality of life by 26 weeks. Similar effects were observed by 26 weeks in the retrospective study. Study extension results (median 114 weeks in study C08-002A/B, C08-003A/B; [redacted]) found that the benefits of treatment were sustained. Almost every patient in the prospective studies (and most in the retrospective study) experienced one adverse event; however, not all were considered by the study investigators to be treatment-related. SAEs associated with eculizumab therapy appeared to be uncommon. Three deaths were observed in the prospective (n=1) and retrospective studies (n=2); however, none were deemed by the study investigators to be related to eculizumab. Similarly, three reports of meningococcal infection with eculizumab treatment in aHUS patients has been reported in prospective (n=2) and retrospective (n=1, post market report) studies.

These findings should however be interpreted with caution. Due to the absence of a control group in all four prospective studies, inference of treatment effects (including magnitude) may be confounded.

Similarly, due to the absence (or clear presentation) of a systematic review (efficacy and safety) of comparator evidence in the MS, outcome differences cannot be examined with the comparators specified in the NICE scope (e.g. plasma therapy, dialysis or transplantation). In addition, AEs deemed to be treatment-related were identified by the study investigators (no details were available on whether safety outcomes were also assessed by an independent endpoint assessment adjudication committee) and as such may have been open to bias. The key uncertainties in the clinical evidence relate to optimal dosing an frequency (no dose-response studies have been undertaken to establish an optimal dose) and duration of treatment (there are no well controlled long-term prospective studies of eculizumab therapy and therefore it is unclear whether all patients need to continue long-term therapy).

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The manufacturer submitted a QALY-based cost-consequence analysis to NICE, undertaken from the perspective of the NHS, to inform judgements about whether eculizumab offers good value for money for the NHS. This analysis took the form of a Markov model based principally on CKD progression. Without discounting, the manufacturer's model indicates that eculizumab is expected to produce an additional 37.65 years of life and 38.47 QALYs compared to standard care per patient. The undiscounted incremental cost of eculizumab versus standard care is estimated to be in excess of [redacted] per patient. When discounted at a rate of 1.5%, the manufacturer's model suggests that eculizumab produces an estimated 24.08 additional years of life and 25.22 additional QALYs compared to standard care per patient. The undiscounted incremental cost of eculizumab versus standard care is estimated to be approximately [redacted] per patient.

The critical appraisal undertaken by the ERG identified numerous problems within the manufacturer's cost-consequence model. The most important of these relates to the highly restrictive structural assumptions of the model, the inappropriate interpretation of evidence relating to the benefits of eculizumab over time, the inappropriate use of evidence to characterise CKD damage for patients receiving standard care, the mathematically inconsistent method for handling competing event risks, and the questionable choice of relevant evidence used to characterise the prognosis of patients receiving standard care. Whilst some of these problems could be resolved within the existing model, other more serious programming issues cannot be rectified within the constraints of the manufacturer's model structure (in particular the handling of competing risks). The ERG takes the view that the manufacturer's model submitted is unlikely to produce robust results hence value in informing decision-making is questionable.

In light of the substantive problems with the manufacturer's model, the ERG developed a new exploratory model. This process was undertaken to allow the ERG to explore the likely impact of making more plausible assumptions about the nature of CKD event hazards over time and to more appropriately handle competing risks. The majority of assumptions made by the manufacturer were retained within the ERG model, although rather than using the pre-treatment data from studies C08-002A/B and C08-003A/B, the ERG model characterises the prognosis of standard care using published aHUS registry data. It should be noted that the outcomes within the registry data may be skewed to favour those patients who received better care as their clinicians made the diagnosis, were aware of the registry, and administered plasma therapy; those patients with aHUS not in the registry may have received a lower standard of care as a result of misdiagnosis, no use of plasma therapy, and therefore had a much poorer outcome. Whilst this is a potentially relevant bias, the same may be true for patients who were recruited into the eculizumab studies compared against those who were not. The ERG model indicates a considerably better prognosis for patients receiving standard care compared with the predictions of the manufacturer's model, hence the incremental QALY gain is estimated to be considerably lower than that suggested by the MS. In addition, the ERG estimate of the incremental cost of eculizumab versus standard care is higher than that presented by the manufacturer.

The ERG notes that the interim process and methods guide for Highly Specialised Technologies highlights concern for the achievement of three types of economic efficiency: productive efficiency, technical efficiency and allocative efficiency. Efficiency arises when benefits are maximised and opportunity costs are minimised. The presentation of disaggregated costs and health benefits is useful and is in line with the HST methods guide. However, the ERG recognises that such disaggregated information does not explicitly address the opportunity costs associated with the decision nor does it indicate whether the incremental net benefit associated with the recommendation for a new technology is expected to be positive.

9.2.2 Cost to the NHS and PSS

In addition to the cost-consequence model, the manufacturer submitted a budget impact model. Based on the manufacturer's analysis, the net budget impact of recommending eculizumab will be approximately [redacted] in 2013, rising to [redacted] in 2017. The overall 5-year predicted net budget impact will be around [redacted] over the period 2013-2017. The ERG believes that the estimates of uptake of eculizumab following a positive NICE recommendation would likely be higher than those assumed by the manufacturer. A re-analysis of the manufacturer's budget impact model

assuming an uptake rate of 100% results in a predicted 5-year net budget impact of in excess of [redacted] over the period 2013 to 2017.

9.2.3 Non-health benefits

The MS[1] includes details of wider societal (non-health) benefits, valued in terms of cost-savings associated with the use of eculizumab. The ERG believes that these estimates are substantially over-estimated due to the inclusion of inappropriate resource items (e.g. transfer payments) and the use of highly unrealistic assumptions. Further, since the manufacturer's societal analysis does not consider the non-health benefits forgone associated with curtailing existing treatments and services to fund eculizumab, the ERG does not consider this analysis to be helpful in informing decision-making.

9.3 Strengths and limitations

9.3.1 Strengths of the MS

The ERG believes that the following represent strengths within the MS:

- The MS contains relevant information relating to the retrospective and prospective studies of eculizumab for the treatment of patients with aHUS.
- The MS also contains details of a recent UK survey sponsored by aHUS UK which provides relevant information concerning the impact of the disease on patients and their families. Some of this information is used to inform the analysis of wider societal benefits.
- The MS includes details of a systematic search used to identify RCTs and single-arm studies of eculizumab for aHUS.
- The MS includes a range of economic information including a QALY-based cost-consequence model, an assessment of the expected costs to the NHS and an assessment of wider societal (non-health) benefits associated with recommending eculizumab.

9.3.2 Weaknesses of the MS

The ERG notes the following weaknesses of the MS:

- The ERG is confident that all relevant studies of eculizumab were included in the MS; however, it is not entirely clear if all relevant comparator studies were identified or included. Relevant outcomes data for the specified comparators have not been systematically reported. Additional evidence in the form of case series (and case studies) was also identified, however, these data were excluded from the manufacturer's review.
- The clinical evidence base for eculizumab is restricted to non-randomised studies with very small sample sizes. The primary endpoints within these studies are intermediate outcomes. There is no direct comparative evidence relating to the benefit of eculizumab versus standard care in terms of long-term patient-relevant outcomes (survival and HRQoL).

- The manufacturer's model suffers from a number of errors. Further, the credibility of the outcomes for patients receiving standard care are questionable, as relevant registry data have not been used to inform the modelled prognosis of patients receiving standard care. The ERG does not believe that the results of the model can be considered robust.
- The manufacturer's budget impact analysis appears to underestimate the likely uptake of eculizumab following a positive recommendation.
- The manufacturer's analysis of wider societal (non-health) benefits includes several inappropriate items and unrealistic assumptions. The analysis does not consider the expected cost-savings lost due to the displacement of other technologies and services in order to fund eculizumab.

9.4 Uncertainties

There exist a number of uncertainties within the current evidence base:

9.4.1 Comparative benefits of eculizumab versus standard care

There currently do not exist any direct head-to-head randomised studies of eculizumab versus any other active comparator. All of the clinical evidence relating to eculizumab presented in the MS takes the form of single-arm studies. Whilst the MS mentions the existence of registry studies, this evidence has not been reviewed systematically.

9.4.2 Long-term patient-relevant outcomes of eculizumab and standard care

The prospective and retrospective studies of eculizumab discussed in the MS are relatively short-term and focus on intermediate endpoints. Whilst these endpoints are clinically relevant, their translation to longer-term patient-relevant outcomes (e.g. survival) is subject to considerable uncertainty.

9.4.3 Comparative HRQoL benefits of eculizumab versus standard care

The available evidence on the impact of eculizumab on patients' HRQoL may be subject to confounding as it is drawn from single arm studies which did not include a control group. The incremental HRQoL benefits of eculizumab versus standard care remain at best, highly uncertain.

9.4.4 Effectiveness and costs of eculizumab in paediatric patients

The evidence base for paediatric populations is comparatively weaker than that for the adult population. Ongoing eculizumab studies may help to elucidate the effectiveness of eculizumab in younger patients.

9.4.5 Optimal treatment duration and frequency strategy

There remains uncertainty with respect to the optimal treatment strategy using eculizumab. There exists no published evidence on alternative dosing to that described in the license or on the use of intermittent treatment to manage flares. As aHUS may follow a relapsing/remitting type of disease course for some patients, continual use of eculizumab may not be necessary once the patient has stabilised (the same is true of plasmapheresis in a proportion of patients). There is also some evidence that patients with certain genetic abnormalities (e.g. MCP) have a better prognosis than others. It should also be noted that indefinite treatment using eculizumab requires fortnightly infusions which will present a burden for some patients. Future research should consider the careful balance of risks and benefits of alternative treatment strategies using eculizumab. Ideally, such research should take the form of randomised controlled trials.

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Appendix 1: ERG corrections to the manufacturer's executable model

The following corrections were made to the manufacturer's model:

1. *Correction of standard care transition probabilities which exceed 1.0:* Worksheet "markov_SOC" cell X33 – formula changed from "=1-R33-Z33" to "=markov_SOC!X13"
2. *Removal of paediatric dose reductions:* Worksheet "Inputs" cells F32:F35 and worksheet "markov_SOC" cells BA25:B141 amended to "0"
3. *Correction of double-discounting of immunosuppressant costs:* Worksheet "markov_SOC" cell A23 – formula changed from =-PV(AT20,AW21,AW20) to "=AW20"
4. *Correction of incorrect discount rates*: Worksheet "Inputs" cells Q25 and Q41 – value amended to "0.035"

Appendix 2: Manual for amending ERG model parameters

(a) Main input parameters

The ERG model is comprised of 11 worksheets. The key model parameter values are contained in the spreadsheet "Parameters." Table A2i below shows the baseline values and cell references for these parameters. Values highlighted with an asterisk (*) are derived from the Solver fitting routine and should not be amended on this worksheet.

Table A2i: Key model parameter values and cell references

Model parameter	Baseline value	Cell reference
Discount rate QALYs	0.035	C6
Discount rate costs	0.035	C7
Population parameters		-
Patient start age	28	C9
Probability female	0.65	C10
Other transition parameters		-
Probability transplant | ESRD – eculizumab	0.00	C12
Probability transplant | ESRD - standard care	0.04	C13
Probability transplant success	0.25	C14
Probability excess death - SC initial event	0.08	C15
Probability excess death - SC subsequent events	0.01	C16
Probability excess death aHUS - SC post-transplant	0.05	C17
Health utilities		-
HRQoL eculizumab CKD0-2	1.00	C19
HRQoL eculizumab CKD3-4	0.87	C20
HRQoL eculizumab CKD5/ESRD	0.87	C21
HRQoL eculizumab transplant	0.66	C22
HRQoL standard care state utility loss	0.21	C23
HRQoL standard care CKD0-2	0.79	C24
HRQoL standard care CKD3-4	0.66	C25
HRQoL standard care CKD5/ESRD	0.66	C26
HRQoL standard care transplant	0.66	C27
State costs (annual except transplantation)		-
CKD0-2	£960.00	C29
CKD3-4	£971.00	C30
CKD5/ESRF	£24,282.00	C31
Transplant cost (one-off)	£18,792.00	C32
Successful transplant maintenance	£6,641.00	C33
Plasmapheresis	£31,148	C34
Cost per dose eculizumab (300mg)	£3,150.00	C35
% admin covered by Alexion Homecare service	0.8	C36
Cost admin	£197.00	C37
Meningococcal vaccine (once-only)	£30.00	C38
First 6-month eculizumab cost (incl induction)	£177,454.40	C39
Subsequent 6-month eculizumab cost (maintenance)	£164,824.40	C40

(b) Re-running the Solver routine for the standard care group

The model solver fitting routine can be re-run using the following steps:

1. Go to the “StandardCare” worksheet
2. In the Excel ribbon (MS Excel 2010) click “Data” and then click “Solver”
3. In the Solver window, click “Solve”

Different initial values can be assigned to the fitted transition probabilities by amending the following cells in the “StandardCare” worksheet: D7, E8, D12, E13, C25, C26, C27. These cells are highlighted in yellow.

(c)Altering the 6-month interval used to extrapolate forward

The base case model uses data from the interval 18-24 months to extrapolate future transitions within the eculizumab group. This can be altered in the “Eculizumab” worksheet by changing which cells are looked up by the transition matrices. The relevant cells are in the range C7:E39.