NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Premeeting briefing

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

This premeeting briefing is a short summary of:
- the evidence and views submitted by the manufacturer, the consultees, and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Evaluation Committee meeting and should be read with the full supporting documents for this evaluation.

Key issues for consideration

Clinical issues

- Is the Committee satisfied that all clinical evidence on the efficacy of eculizumab and comparator treatments has been identified?
- Is there sufficient clinical evidence provided to make recommendations on the use of eculizumab in children?
- Are there any differences between the clinical subtypes of aHUS in terms of the likely response to eculizimab?
- What is the likely dosing regimen and duration of treatment with eculizumab in clinical practice?
- Do the data provide sufficient information to anticipate the likely long-term effects of eculizumab therapy?

Value issues

- What are the preferred values for likely net cost/patient, net benefit/ patient and total cost of the technology?

- How do these values compare with values for other technologies currently provided under Specialised Commissioning (and therefore potentially could be displaced)?
- How do changes in non-NHS/PSS costs with the technology compare with those for other Specialised Commissioning Technologies?
- Is the preferred "total cost" reasonable in the context of R&D and manufacturing costs for this technology?
- Are there any significant benefits of treatment, other than health-related outcomes, which have not been taken into account in the economic analysis?

1 Nature of the condition

1.1 Patients with aHUS have chronic uncontrolled complement activation causing on-going platelet, endothelial and white blood cell activation, leading to inflammation and thromboses (blood clots) in small blood vessels throughout the body, a process known as systemic thrombotic microangiopathy (TMA). As a result of ongoing complement-mediated TMA, patients with aHUS are at constant risk of sudden and progressive damage and failure of multiple vital organs. aHUS can occur at any age, from the neonatal period to adult age. Onset during childhood (≤ 18 years) appears slightly more frequently 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.

1.2 There is uncertainty with respect to the number of patients with aHUS in the UK. The manufacturer's submission quotes an incidence estimate of 5.5 persons per million based on the

estimated prevalence in NHS North East, and a prevalence estimate of 0.60 persons per million.

1.3 Mortality rates for aHUS range from up to 10 to 15% during the acute phase and up to 50% in later stages with progression 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 adults. aHUS and its treatment may severely impair health-related quality of life (HRQoL).

1.4 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 manufacturer's submission suggests that current treatments for aHUS are ineffective in reducing morbidity and mortality. The manufacturer's submission recognises that transplantation (kidney or liver-kidney) is generally not recommended due to the high risks of graft loss in these patients.

1.5 In 2013, aHUS UK sponsored a UK survey 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. which 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 The technology

2.1 Eculizumab (Soliris) is a human monoclonal antibody to complement C5, which blocks pro-thrombotic and pro-inflammatory processes. It is produced from murine myeloma cells by recombinant DNA technology. Eculizumab received a UK marketing authorisation in September 2011 “in adults and children for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS)”. It is also licenced for use in patients with paroxysmal nocturnal haemoglobinuria.

2.2 Eculizumab is administered intravenously in adults as initial treatment for 4 weeks, then as maintenance treatment as shown in the table below. The Summary of Product Characteristics (SmPC)

for eculizumab states that “treatment is recommended to continue for a patient’s lifetime, unless the discontinuation of treatment is clinically indicated.”

Method of administration	Intravenous (IV) infusion at a final concentration of 5 mg/ml
Dosing (Adults)	Initial phase: 900mg eculizumab administered via IV infusion every week for the first 4 weeks Maintenance phase: 1200mg eculizumab administered via IV infusion on the fifth week, followed by 1200mg IV infusion every 14 ± 2 days
Dosing (Children)	Patients with a body weight ≥40kg are treated in line with the adult dosing recommendations. Paediatric patients with a body weight below 40kg have their dose adjusted according to body weight. See SmPC.

2.3 Following the launch of eculizumab in the UK in November 2011, use was restricted to individual patient funding through the primary care trust individual funding request process until April 2013. NHS England then implemented an interim policy whereby eculizumab was funded for all newly diagnosed patients with aHUS. This policy was subsequently extended to all patients with aHUS after a review was conducted by the Clinical Priorities Advisory Group, who recommended that funding should also be made available to patients on dialysis to enable a successful renal transplant to be undertaken. Eculizumab is currently commissioned by NHS England in line with the Clinical Commissioning Policy Statement (published in September 2013) for:

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

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

The commissioning policy is considered interim until NICE is able to offer definitive advice. The policy is currently administered through an interim national aHUS service in Newcastle, and statements from professional consultees confirm that all of the components necessary to deliver eculizumab within a national specialised service are already in place and functioning.

2.4 The summary of product characteristics lists the most common adverse reactions of eculizumab in adults as headache and leukopenia. The safety profile in adolescents (patients aged 12-17 years) is consistent with that observed in adults. The most common adverse reactions reported in paediatric patients (aged 2 months to 11 years) are diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache. Due to its mechanism of action, the use of eculizumab increases the patient's susceptibility to meningococcal infection. To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving eculizumab. All patients in the UK receiving eculizumab should receive long-term prophylactic antibiotics with penicillin (or erythromycin if they are allergic to penicillin). Statements from clinical consultees indicated that they have seen very few adverse reactions that affect either the management of the condition or the quality of life of the patient since using eculizumab. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.5 Patient experts consider that the impact of eculizumab is influenced by the severity of the disease and the stage of life when a patient becomes affected. For patients with aHUS who have kidney failure, eculizumab offers them the potential for a kidney transplant and

therefore an opportunity to restore their health and have a life free from the restrictions of treatment. For patients with active disease, eculizumab offers them the possibility of avoiding end stage renal failure, dialysis and kidney transplants as well as other organ damage. It also offers patients the chance to restore kidney function or retain their residual kidney function without the need for further treatment.

3 Remit and decision problem

3.1 The remit from the Department of Health for this evaluation was: "To evaluate the benefits and costs of eculizumab within its licensed indication for the treatment of atypical haemolytic uraemic syndrome for national commissioning by NHS England."

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Children and adults with atypical haemolytic uraemic syndrome	Clinical evidence relates to children and adults with aHUS. Economic model from manufacturer relates only to the costs and health outcomes for an adult population.
Intervention	Eculizumab	Eculizumab
Comparators	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	Standard care – assumed by manufacturer to include plasma therapy. Kidney dialysis and transplantation are assumed to reflect part of the treatment pathway and are not evaluated as individual comparators. Kidney-liver transplantation is not considered in model.
Outcomes	• overall survival • time to disease recurrence • response to treatment • avoidance of dialysis • avoidance of plasma therapy • maintenance or improvement in kidney function • other major non-renal clinical outcomes • eligible for/success of transplantation • development of antibodies and resistance • adverse effects of treatment • health related quality of life (for patients and carers)	Data not available for: • time to disease recurrence and • eligible for/success of transplantation.

4 Impact of the new technology

4.1 The manufacturer performed a review of clinical evidence for eculizumab and identified two published (C08-002A/B, C08-003A/B) and two unpublished (interim data from C10-003 and C10-004) prospective studies and one retrospective observational study (C09-001r). No randomised controlled trials were identified.

4.2 All prospective studies were 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 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. A summary of the studies is shown in the table below.

Study	**Design**	**Number treated (enrolled)**	**Intervention**	**Primary Outcome**	**Study Duration**
C08-002 A/B Published (Legendre *et al* 2013)	Phase II, open-label non-randomised, prospective, single arm study	17 (17) Adults and adolescents	Eculizumab (900mg IV once weekly (wks 1-4), then 1200mg IV once every 2wks (wk 5 and after)	Reduction of TMA measured by change in platelet count from baseline and haematologic normalisation	26 weeks. All patients allowed to continue in long-term extension trial until product registered and available
C08-003 A/B Published (Legendre *et al* 2013)	Phase II, open-label non-randomised, prospective, single arm study	20 (23) Adults and adolescents	Eculizumab (900mg IV once weekly (wks 1-4), then 1200mg IV once every 2wks (wk 5 and after)	Reduction of TMA measured by TMA-event free status and haematologic normalisation	26 weeks. All patients allowed to continue in long-term extension trial until product registered and available
C10-003 Unpublished	Phase II, open-label non-randomised, prospective,	22 (NR) Children	Eculizumab fixed dose, multiple weight-based	Complete TMA response confirmed by 2 consecutive measurements	26 weeks. All patients allowed to continue in long-term extension trial

	single arm study		dosing regimens		until product registered and available
C10-004 Unpublished	Phase II, open-label non-randomised, prospective, single arm study	41 (NR) Adults	Eculizumab (900mg IV once weekly (wks 1-4), then 1200mg IV once every 2wks (wk 5 and after)	Complete TMA response confirmed by 2 consecutive measurements	26 weeks. All patients allowed to continue in long-term extension trial until product registered and available
C09-001r Published as abstract and results in EPAR	Retrospective, chart review	30 (30) Adults, adolescents and children	Adults and adolescents: Eculizumab (900mg IV once weekly (wks 1-4), then 1200mg IV once every 2wks (wk 5 and after) Children: dosing in weight bands	Reduction in TMA as measured by change in platelet count from baseline, TMA-event free status and difference in TMA intervention rates (pre- and during treatment)	Variable.

4.3 The two prospective clinical studies (C08-002A/B and C08-003A/B) were conducted in two distinct populations of aHUS patients with clinically different baseline characteristics and different expected clinical outcomes. Study C08-002A/B accrued patients in the early phase of aHUS with evidence of severe TMA manifestations with acute worsening of renal function. In these patients eculizumab is expected to control the TMA process, prevent further severe TMA manifestations, and reverse kidney damage. Study C08-003A/B accrued patients with long term aHUS with apparent control of the TMA process due to chronic plasma therapy. Those patients had a long, sustained renal impairment prior to entering the trial. In this population eculizumab is expected to control the TMA process despite discontinuation of plasma therapy and also maintain kidney function. 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. A summary of the results are shown in the tables below (adapted from ERG report pages 43, 45 and 48).

Study	Efficacy variables				Thrombotic microangiography			
	Change in platelet count (x 10^9/L) from baseline, mean (95%CI)	Normalisation of platelet count, n (%)	TMA event-free status, n (%)	Haematologic Normalization, n (%)	TMA intervention rate		Complete TMA response, n (%)	Change in Hb > 20g/L, n (%)
					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	91 (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	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	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	NR	19/20 (95%)	17/20 (85%)	18/20 (90%)	-	0 (0; 0); p<0.0001	7/20 (35%)	10/20 (50%)
114 weeks	NR	18/20 (90%)	19/20 (95%)	18/20 (90%)	-	0 (0; 0); p<0.0001	11/20 (55%)	13/20 (65%)

Study	**Efficacy variables**		**Thrombotic microangiography**				**Renal function**
	Normalisation of platelet count, n (%)	TMA event-free status, n (%)	TMA intervention rate		Complete TMA response, n (%)	Change in Hb > 20g/L, n (%)	eGFR improvement ≥15 mL/min/1.73 m^2, 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%)

Study	Efficacy variables		Thrombotic microangiography					
	Normalisation of platelet count, n (%)	TMA event-free status, n (%)	Complete TMA response, n (%)	Complete TMA response with preservation of renal function	Modified complete TMA response with improvement of renal function	Complete hematologic response	LDH normalisation	Change in Hb > 20g/L, n (%)
C10-003 (n= 22)								
26 weeks	21/22 (96%)	NR	14/22 (64%)	NR	NR	18/22 (82%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C10-004 (n=41)								
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 text is academic in confidence.

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

4.4 In the two published 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 adverse event 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). 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).

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

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

[redacted] In retrospective study C9-001r, 13 patients discontinued eculizumab therapy. Reasons for discontinuation included 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.

4.7 The adverse events data in the manufacturer's submission (pages 102-107) were limited to treatment-related adverse events. Although nearly all patients reported one adverse event 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 adverse event that was considered by the study investigators to be study drug-related (reported as definite, probable or possible). Treatment-related adverse events 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 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 serious adverse events (C08-002A/B: n=3; C08-003A/B: n=2). Leucopoenia, nausea, vomiting and accelerated hypertension were the most common treatment-related adverse events in study C08-002A/B, whereas headache, leucopoenia and lymphopenia were the most common treatment-related adverse events in study C08-003A/B.

4.8 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) provided a

similar adverse event profile for treatment related adverse events. The most notable difference was that the number of patients who reported drug-related ‘infections and infestations’ increased from four patients to eight patients at update. The number of severe treatment-related adverse events did not increase between the original study and extension period. Only one severe adverse event (influenza) which had not been previously reported was observed in the extension period of study C008-003A/B. 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 manufacturer’s submission page 107). Both infections resolved with appropriate treatment, although one led to permanent discontinuation of eculizumab treatment and withdrawal from the study.

4.9 Five registry sources for patients with aHUS on standard care are mentioned in the manufacturer’s submission and were described in more detail in the ERG report, as summarised in the table below. Outcomes are reported at different time points therefore comparison between the registries at individual time points is not possible. However the information is useful to provide an insight into the prognosis of patients receiving standard care.

Registry	Patient population	Treatments	Duration of follow-up	Survival		ESRD		Relapse		Remission	Successful transplant	
				Child	Adult	Child	Adult	Child	Adult		Child	Adult
Coppo et al (2010)	Adult patients experiencing TMA N=241 54 detectable ADAMTS13 activity	Plasma infusion, steroids, rituximab, vincristine, splenectomy	Mean follow-up 17.8 months		87%		21%		14%			
Hovinga et al (2010)	TTP registry – adult and paediatric patients N = 261 (patients who had ADAMTS13 activity measured at initial diagnosis) 201 - ADAMTS13 ≥10%	Plasma exchange	Median follow-up 4.6 years	68%		NR		4%				
Fremeaux-Bacchi et al (2013)	aHUS diagnosed adult and paediatric patients– excluded secondary aHUS (except in pregnancy) N= 214 89 child; 125 adults	High and low frequency plasma exchange	1 month	87/89 (98%)	125 (100%)	13 (15%	57 (46 %)	-		-		
			1 year	83/89 (93%)	124/125 (99%)	20 (23%)	69 (55 %)	16/65 (25%)		19/65 (29%)		
			5 years	83/89 (93%)	124/125 (99%)	26 (29%)	79 (63 %)	12/65 (18%)		3/65 (3%)		
			Last follow up	82/89 (92%) – 14yrs	123/125 (98%) – 7yrs	28 (32%)	87 (70 %)	-		-		
Noris et al (2010)	aHUS diagnosed adult and paediatric patients N=273	Plasma exchange, transplant	Up to 10 years – outcomes reported after initial episode and 3 years	92% (outcome of initial episode); 89% at 3 years		36% (outcome of initial episode); 45% at 3 years				60% (outcome of initial episode); 46% at 3 years	33% (1-yr post transplant)	45% (1-yr post transplant

5 Cost to the NHS and personal social services and Value for money

5.1 The manufacturer developed 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. 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) and its impact in terms of costs, HRQoL and survival. Chronic kidney disease 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 sensitivity analyses and probabilistic sensitivity analysis.

5.2 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 (see table below).

Outcome	Eculizumab	Standard care	Incremental
Undiscounted results			
LYGs	47.62	9.97	37.65
QALYs	45.06	6.59	38.47
Cost	[redacted]	[redacted]	[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]	[redacted]	[redacted]

Redacted text is Commercial in Confidence

5.3 The manufacturer's 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. The probabilistic sensitivity analyses are shown below, and 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.

Outcome	**Eculizumab**	**Lower 95% crl**	**Upper 95% crl**	**Standard care**	**Lower 95% crl**	**Upper 95% crl**
QALYs	31	28.4	32.7	5.9	2.6	8.7
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Redacted text is Commercial in Confidence

5.4 The ERG raised several concerns about the manufacturer's economic analysis regarding the suitability of the model structure, the integrity of the pre-model analysis and the robustness of the manufacturer's model results.

5.5 To explore these issues, the ERG developed 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. Results from the ERG model suggest 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.

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]	[redacted]	[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]	[redacted]	[redacted]

Redacted text is Commercial in Confidence

5.6 The manufacturer also developed a budget impact model to estimate the total costs of eculizumab 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 [redacted] each year. Based on the manufacturer's analysis, the net budget impact of recommending eculizumab is estimated to be approximately [redacted] in 2013, [redacted] in 2017. The overall 5-year predicted net budget impact will be [redacted] over the period 2013-2017.

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

6 Impact of the technology beyond direct health benefits and on the delivery of the specialised service

6.1 The manufacturer included in its submission 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.

6.2 The ERG considered that the manufacturer's estimates of non-health benefits are over-estimated due to the inclusion of inappropriate resource items (e.g. transfer payments) and the use of what they considered to be 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 questioned the usefulness of this analysis.

7 Equalities issues

7.1 No equality issues were raised during scoping or in the evidence submissions.

8 Authors

[redacted]

Technical Advisor

with input from the Lead Team and Committee Chair:

Anthony Wierzbicki (clinical lead), Ron Akehurst (value lead), Mark Sheehan (lay lead), and Peter Jackson (Chair of HST Evaluation Committee).