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Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) [ID703]

Dear [redacted]

The Evidence Review Group, ScHARR, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th September by Alexion. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to this letter to the Institute by **5pm** on **Friday 18 October 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] Technical Advisor ([redacted]@nice.org.uk). Any procedural questions should be addressed to [redacted], Project Manager ([redacted]@nice.org.uk) in the first instance.

Yours sincerely

[redacted]
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

1. **Priority question:** The submission includes a systematic review of non-randomised evidence for eculizumab. Why does the submission not also include a systematic review of interventions used as standard care (i.e. the comparators listed in the NICE scope)? For example this might include studies such as Hovinga et al 2010, Coppo et al 2010 and Noris et al 2010.

   Alexion Response:
   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.

   Below, we provide some examples from our September submission explaining how the use of SOC methods, prior to the availability of eculizumab, are inadequate and leave patients at continued risk of progression to end-stage renal failure (ESRF), dialysis, and early mortality.

   - Alexion Submission Page 31: "The disease affects both children and adults and has a very poor prognosis, demonstrated by the fact that 33% to 40% of aHUS patients die or progress to end-stage renal failure (ESRF) requiring dialysis with the first clinical manifestation.(Caprioli et al, 2006; Noris et al, 2010) The chronic nature of aHUS results in progressive, on-going morbidity as 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on plasma exchange or plasma infusion (PE/PI) or dialysis and a progressive increased mortality rate thereafter."

   - Alexion Submission Page 31: "Long-term data have shown a mortality rate of 32% at 4.4 years median follow-up.(Hovinga et al, 2010) The significant morbidity and mortality associated with aHUS represents an unmet medical need for patients with an ultra-rare and life-threatening disorder." [Please note: All patients in the Hovinga et al database received SOC (PE/PI) at the time of diagnosis of their TMA. Thus, this dataset provides medical evidence of a 32% mortality rate with PE/PI as a SOC method prior to the availability of eculizumab.]

   - Alexion Submission Page 128: "Medical evidence demonstrates that despite the use of supportive care [PE/PI], there is a progression of aHUS, continued on-going risk of TMA, and life threatening complications for aHUS patients.(Noris and Remuzzi, 2009; Noris et al, 2010; Hovinga et al, 2010; Legendre et al, 2013; SmPC, 2013)"

   - Alexion Submission Page 139: "aHUS is a progressive and life-threatening disease with 33% to 40% of patients reaching ESRF or death following the diagnosis. In two TMA registries (described in Coppo et al 2010 and Hovinga et al 2010) [where all patients were receiving SOC], mortality of aHUS patients (TMA with ADAMTS13 >10%) reached 13% (17.8 month mean follow up) and 32% (4.4 year median follow up), respectively. Further, the percentage of patients with reported acute renal failure was 21% and 54%, respectively, exemplifying the life-threatening and progressive nature of aHUS."

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- Alexion Submission Page 139: "The Coppo and Hovinga datasets consist of adults with confirmed ADAMTS13 activity and no Shiga-Toxin producing enterohaemorrhagic Escherichia coli (STEC) infection, which is closely aligned to both the proposed clinical pathway of care and the eculizumab clinical trials population. Therefore, both the Coppo and Hovinga datasets present a realistic expectation of aHUS presentation and outcomes in adults."

2. **Priority question:** Please provide further details about subsequent treatments used in the clinical trials. For example, in instances whereby patients withdrew from the studies, did they continue using eculizumab? What happened to these patients?

Alexion Response:

C08-002 and C08-003: Among 37 patients included in the C08-002 and C08-003 prospective trials, 5 patients discontinued eculizumab, with 1 out of 5 patients experiencing TMA after discontinuation. A summary of these five patients is as follows:

- One patient discontinued after one dose of eculizumab due to protocol violation (Systemic Lupus Erythematosus (SLE) diagnosis). No follow-up is available for this patient.
- One patient discontinued after four doses of eculizumab due to a non-drug-related adverse event (pancytopenia). This patient was deceased as of last follow-up (based on personal communication with the investigator).
- Three patients who had met all endpoints discontinued after 26 weeks. Of these:
    - One patient experienced TMA complications 80 days after discontinuation including renal impairment which was recovered after re-starting eculizumab;
    - One patient who became dialysis-free during the study had no loss of kidney function as of last follow-up 8 weeks post discontinuation; and
    - One patient was lost to follow-up after returning to his native country.

C09-001r: In this retrospective trial, patients were not treated according to the prospective clinical trial or later FDA-approved dosing. Among the 30 paediatric and adult patients, 13 patients discontinued eculizumab, with 4 patients experiencing TMA manifestations after discontinuation. Three of these patients restarted eculizumab, while the fourth received only one dose and did not continue after rapidly progressing to ESRF.

Among the [redacted] discontinuations from the retrospective trial:

- Two deaths occurred; [redacted]
- Two discontinued due to on-going dialysis prior to and during eculizumab; and
- Three patients have no additional information after 5-221 days of follow-up.

C10-003: [redacted].

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C10-004: Three patients discontinued eculizumab prior to the completion of the 26-week study period. [redacted].

3. **Priority question:** For the primary outcome of each study (studies C08-002, C08-003, C09-001r, C10-003 and C10-004) please provide Kaplan-Meier curves.

   Alexion Response:
   Kaplan-Meier curves are provided in Appendix 1 for the following outcomes in each of the clinical studies C08-002, C08-003, C09-001r, C10-003, and C10-004:

   1. Time to Platelet Count Normalization in C08-002;
   2. Time to TMA Event-Free Status in C08-002;
   3. Time to TMA Event-Free Status in C08-003;
   4. Time to Platelet Count Normalization in C09-001r;
   [redacted]

4. **Priority question:** Section 9.1.2 Page 60 - Why were relevant clinical data not obtained or included from unpublished studies that were not sponsored by Alexion? Were the authors of these studies contacted? If not, why?

   Alexion Response:
   It is not clear to Alexion exactly which unpublished studies the reviewer is referring. The data provided in our submission comes from four prospective clinical studies and one retrospective eculizumab study (C09-001r), each of which attempted to collect data from all patients on eculizumab prior the commercial availability of eculizumab. Specifically, physicians receiving drug for patients through the Alexion-sponsored compassionate use program were contacted to engage in clinical review and participation in the Alexion C09-001r trial, a retrospective, observational, non-interventional trial of patients who had been identified as meeting the diagnosis of aHUS and had received at least one dose of eculizumab outside of an Alexion-sponsored controlled clinical trial. Data from 30 of 36 patients were included in this retrospective trial. A total of six patients were not included in the trial because they declined to participate—two patients declined participation and the treating physicians for four other patients declined participation. Therefore, all data provided include unpublished data with the assurance that patient data are reliable, sufficient, and followed to ensure proper efficacy and safety evaluation.

   NICE Please Note: In our initial set of responses submitted on October 18th, we incorrectly noted in the responses to Questions 4 and 7 that patients enrolled in the C09-001r retrospective data collection were all receiving eculizumab through the Alexion-sponsored compassionate use program; our apologies. More than half of the patients in this study received eculizumab through a commercial purchase; however, this does not impact the clinical data results in any way.

5. **Priority question:** Which criteria were used to determine whether plasma exchange/infusion and dialysis was required for individual patients in studies C08-002, C08-003, C10-003 and C10-004? How many patients received plasma exchange/infusion in each of these studies? Also, Table C8 page 84 details the number

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of patients receiving PE/PI during the current aHUS event - did these patients receive plasma exchange/infusion whilst they were also receiving eculizumab?

Alexion Response:
In clinical practice, there are no evidence-based criteria for physicians to initiate PE/PI in patients with aHUS. Historically—prior to the availability of a clinically proven safe and effective treatment, eculizumab—once the diagnosis of aHUS was made, physicians would choose to use PE/PI, despite the lack of evidence of effectiveness, tolerable safety, or a positive risk/benefit ratio for such treatment. The prospective eculizumab clinical trials included aHUS patients receiving and not receiving PE/PI prior to initiation of eculizumab treatment. Multiple published case studies, and the results of the eculizumab prospective clinical trials, demonstrate that most physicians will not use PE/PI once the patient begins eculizumab treatment since PE/PI does not address the chronic uncontrolled complement activation, and thus the underlying complement-mediated TMA, which causes the morbidities and mortality in patients with aHUS.

Entry Criteria for Trials C08-002 and C08-003
The entry criteria for studies C08-002 and C08-003 required patients to have PE/PI during a screening period. PE/PI administration was up to the discretion of the treating physician prior to study enrolment. The study entry criteria required specific platelet count, haemolysis (as measured by lactate dehydrogenase (LDH) levels), and evidence of organ damage (measured by serum creatinine levels) while receiving PE/PI, as described further below. Dialysis was not an entry requirement for either of these two trials. Further, the need for dialysis was based on physician discretion to manage renal failure prior to and during eculizumab treatment.

C08-002: Patients were eligible for the trial if they had evidence of progressive TMA after four or more sessions of PE/PI in the week prior to enrolment.(Legendre et al 2013) All but a single patient (16/17; 94%), who could not undergo PE/PI because of its adverse effects, received PE/PI and 5/17 patients (29%) were receiving dialysis prior to initiation of eculizumab.

C08-003: Patients were eligible for the trial if they had no decrease in platelet counts of more than 25% for at least 8 weeks before they received the first dose of eculizumab, and were being treated with PE/PI at least once every 2 weeks, but no more than 3 times per week.(Legendre et al 2013) All patients (20/20; 100%) received PE/PI and 2/20 patients (10%) were receiving dialysis prior to receiving eculizumab.

Entry Criteria for Trials C10-003 and C10-004
For the C10-003 trial, patients could receive no more than five weeks of PE/PI prior to enrolment. For the C10-004 trial, there was no requirement for PE/PI or dialysis prior to initiating eculizumab treatment. Additionally, no patients were required to receive PE/PI before trial enrolment. For both trials, patients were excluded if they were receiving chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESRF).

NICE Please Note: We have provided some additional clarification to the above paragraph labelled "Entry Criteria for Trials C10-003 and C10-004" included in our October 18th response and have revised it accordingly. Specifically, we note that for the C10-003 trial, patients could receive no more than five weeks of PE/PI prior to

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enrolment, and we specify the exclusion criteria related to dialysis for both the C10-003 and C10-004 trials.

C10-003: In the prospective C10-003 paediatric study, 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.

C10-004: In the prospective C10-004 adult aHUS study, 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.

Use of PE/PI and Dialysis During Clinical Trials
As defined in the clinical protocol, if at any time during the clinical trials, platelet counts decreased below 40 x 10^9/L or new neurological, renal, or other clinical sign(s) arose, PE/PI could be administered at the investigator's discretion.

C08-002: 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 study because of protocol violation); the other patient received 17 plasma exchanges without interrupting eculizumab treatment.

C08-003: A single patient (1 out of 20 patients; 5%) received a single dose of PE/PI without interrupting eculizumab treatment during the study.

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C10-003: [redacted].

C10-004: [redacted].

[redacted]. It is evident that aHUS is characterized by uncontrolled complement activation and subsequent TMA and end-organ damage such as kidney failure, and while the demonstrated evidence that the effect of eculizumab to inhibit complement activation is immediate, the first appearance of reversal of organ damage most commonly requires a more extended period of treatment time. Indeed, following commencement of chronic eculizumab treatment, renal function should stabilize and the improvement in renal function may be immediate or gradually improve over time with continued life-long therapy. This is evidenced in the C08-003 trial where long-term treatment with eculizumab led to significant renal improvement (eGFR ≥15 ml/min/1.73m^2) and reduction/elimination of proteinuria (representing on-going kidney damage) in 40% of patients over one to two years of treatment, consistent with the observed long-term chronic inhibition of complement activation in patients with aHUS properly dosed with chronic eculizumab treatment.

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6. **Priority question:** How were patients identified for recruitment into studies C08-002, C08-003, C10-003 and C10-004? Were consecutive patients recruited or was a convenience sample used? Please provide as much detail as possible on the selection process.

   Alexion Response:
   All study participants for clinical programs C08-002 (74 study sites), C08-003 (69 study sites), C10-003 (46 study sites) and C10-004 (42 study sites) were recruited consecutively and enrolled by the investigator at his/her respective study site. As expected in an ultra-rare disease trial, not all open study sites identified aHUS patients during the study enrolment period.

7. **Priority question**: Please provide information relating to planned dose and actual dose received (including reasons for deviation) in studies C08-002, C08-003, C09-001r, C10-003 and C10-004. Are there any data from these studies relating to a dose-response relationship? Is there any evidence to support flexible dosing?

   Alexion Response:
   NICE Please Note: After further review of available reports, we are able to provide more detailed information about dosing in the eculizumab clinical trials so have revised our response to Question 7 accordingly. We provide these details, and any necessary clarifications to our original response, in red below.

   In the prospective trials C08-002, C08-003, C10-003, and C10-004, all patients were required to receive doses of eculizumab according to the regimen described in the protocol. In C08-002 and C08-003, there were no protocol violations due to alternative dosing and there is no evidence to support flexible dosing. [redacted]. Data from the prospective C10-003 and C10-004 studies are still being analysed (only interim analyses are complete) and therefore dosing information has not been validated.

   C08-002: [redacted].

   [redacted]

   [redacted].

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C08-003: [redacted]

C09-001r: As described above and in our September submission, study C09-001r was a retrospective, observational, non-interventional trial of patients with aHUS who met the diagnosis of aHUS and had received at least one dose of eculizumab prior to initiation of Alexion-sponsored controlled clinical trial through the Alexion pre-approval compassionate use program. As this was a non-study treatment protocol, the dosing regimen was not specified; the duration of usage varied among patients, ranging from a single dose to chronic therapy, at the treating physician's discretion. [redacted]. We reiterate that these patients were treated outside of a clinical trial setting and the eculizumab doses administered were at the discretion of the treating physician. [redacted].

NICE Please Note: As previously stated in Question 4, in our initial set of responses submitted on October 18th, we incorrectly noted in the responses to Questions 4 and 7 that patients enrolled in the C09-001r retrospective data collection were all receiving eculizumab through the Alexion-sponsored compassionate use program; our apologies. More than half of the patients in this study received eculizumab through a commercial purchase; however, this does not impact the clinical data results in any way.

All available pharmacokinetic and pharmacodynamic data for eculizumab from C08-002, C08-003, and C09-001r were simultaneously modelled. These models validate the selection of eculizumab 900 mg IV every two weeks for the induction period and 1200 mg IV every two weeks for the maintenance for this study. There is no analysis that

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provides evidence to support flexible dosing in any patient setting. In contrast, there are observed serious and potentially life-threatening medical complications with dose disturbances as recognized in the Statement of Product Characteristics (SmPC), which states that 5 out of 18 patients who discontinued chronic eculizumab treatment experienced a TMA. Of the nine patients who prematurely discontinued eculizumab treatment (eligible to continue treatment in the trials), five patients demonstrated clinical evidence of TMA following eculizumab withdrawal as of the last available follow-up visit.

Therefore, there is clear medical evidence, as reflected in the SmPC, that altering the eculizumab dosing regimen will cause serious and potentially life-threatening complications in aHUS patients.

8. **Priority question:** Please provide details of adherence rates to protocol specified doses of eculizumab in prospective studies C08-002, C08-003, C10-003 and C10-004.

Alexion Response:
Adherence rates for the prospective trials C08-002 and C08-003 are not available at this time. [redacted]. The calculated adherence rates will be provided to NICE as soon as possible.

Dosing information for trials C10-003 and C10-004 has not yet been validated since only interim analyses of these trials are currently available. It is therefore not possible to examine dosing adherence rates for the C10 studies at the present time.

9. **Priority question:** Section 9.6 Table C11. Where appropriate (e.g. CKD state) please provide baseline and final values for studies C08-002, C08-003, C09-001r, C10-003 and C10-004. For all outcomes in Table C11 please state how many patients provided data for each analysis. Were there any missing data and how were they dealt with?

Alexion Response:
The following tables show data regarding platelet count, lactate dehydrogenase (LDH) levels, eGFR, haemoglobin, health-related quality of life (HRQoL), and chronic kidney disease (CKD) stages at baseline, 26 weeks, 1 year, and 2 years for the five studies, where applicable. The numbers of patients are presented for each visit. Not all patients have data points for each data value at every visit, particularly at years 1 and 2. Table C11 in our September 2013 aHUS NICE submission presented least square (LS) means and P-values from repeated measures analyses. The missing observations were handled by the mixed effect model method.

C08-002:

	Baseline	Change from Baseline		
		26 weeks	1 year	2 years
Platelet Count (x10^9/L)	[redacted]	[redacted]	[redacted]	[redacted]
LDH (U/L)	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73xm^2)	[redacted]	[redacted]	[redacted]	[redacted]

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	Baseline	Change from Baseline		
		26 weeks	1 year	2 years
Hemoglobin (g/L)	[redacted]	[redacted]	[redacted]	[redacted]
EuroQol 5D Measurements*	[redacted]	[redacted]	[redacted]	[redacted]

*Variable is the index scored using the US Time Trade-Off (TTO) value set

C08-003:

	Baseline	Change from Baseline		
		26 weeks	1 year	2 years
Platelet Count (x10^9/L)	[redacted]	[redacted]	[redacted]	[redacted]
LDH (U/L)	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73xm^2)	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin (g/L)	[redacted]	[redacted]	[redacted]	[redacted]
EuroQol 5D Measurements*	[redacted]	[redacted]	[redacted]	[redacted]

*Variable is the index scored using the US Time Trade-Off (TTO) value set

C09-001r:

	Baseline	Change from Baseline
		26 Weeks
Platelet Count (x10^9/L)	[redacted]	[redacted]
LDH (U/L)	[redacted]	[redacted]
eGFR (mL/min/1.73xm^2)	[redacted]	[redacted]
Hemoglobin (g/L)	[redacted]	[redacted]

C10-003:

	Baseline	Change from Baseline	
		26 Weeks	1 Year
Platelet Count (x10^9/L)	[redacted]	[redacted]	[redacted]
LDH (U/L)	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73xm^2)	[redacted]	[redacted]	[redacted]
Hemoglobin (g/L)	[redacted]	[redacted]	[redacted]

C10-004:

	Baseline	Change from Baseline	
		26 Weeks	1 Year
Platelet Count (x10^9/L)	[redacted]	[redacted]	[redacted]

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	Baseline	Change from Baseline	
		26 Weeks	1 Year
LDH (U/L)	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73xm^2)	[redacted]	[redacted]	[redacted]
Hemoglobin (g/L)	[redacted]	[redacted]	[redacted]

Summary of CKD Stages:

Study	Visit	CKD Stages (Number of patients)
C08-002	[redacted]	[redacted]
C08-003	[redacted]	[redacted]
C09-001r	[redacted]	[redacted]
C10-003	[redacted]	[redacted]
C10-004	[redacted]	[redacted]

10. **Priority question:** Section 9.6. Please provide mortality data for the extension periods in studies C08-002 and C08-003 separately (the value for money section suggests 1 death in 3 years in both studies combined?).

Alexion Response:
The following table provides an update based on the 3-year data for duration of exposure to eculizumab and total number of deaths. These data confirm the mortality rate provided in our September 2013 submission of 1 death [redacted]. As noted, the death was determined not to be related to eculizumab.

Study	C08-002 (n=17)	C08-003 (n=20)	C08-002 & C08-003 (n=37)
Date of Database Lock	[redacted]	[redacted]	[redacted]
Duration of Exposure (yrs) Mean (SD) Median Minimum, Maximum Patient-Years	[redacted]	[redacted]	[redacted]
Number of Deaths	0	1	1

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11. **Priority question:** Page 110 - The SmPC recommends lifetime treatment, please provide the evidence to support this.

Alexion Response:

The European Medicines Agency (EMA) recognizes the chronic nature of aHUS and the on-going substantial risk of mortality and significant morbidities as a result of the disease; specifically, the medical evidence that 33% to 40% of aHUS patients die or progress to ESRF with standard of care (SOC). The first clinical manifestation of thrombotic microangiopathy (TMA) in a patient with aHUS leads to a life-long and constant risk of sudden and progressive injury and failure of multiple organs including the kidneys, brain, heart, lungs and organs of the gastrointestinal system. Any and all of these failures can ultimately lead to severe morbidity and premature death.(Noris et al, 2010; Sellier-Leclerc et al, 2007; Neuhaus et al, 1997; Noris and Remuzzi, 2009) While the disease may appear to be in "remission" at any given time, the sudden onset of acute and potentially life threatening illness is an omni-present, lifelong risk without eculizumab. In addition, since aHUS is due to genetic mutations in the complement regulatory system that leads to systemic complement-mediated TMA and organ damage, EMA also recognizes that SOC does not address the on-going, life-long systemic complement-mediated TMA.

As noted in Question 10 above, EMA evaluated the eculizumab registration trials (C08-002, C08-003, and C09-001r) and followed 9 of 18 patients that prematurely discontinued from chronic eculizumab treatment. Of these nine patients, five patients demonstrated clinical TMA following eculizumab withdrawal at the last follow-up visit. Therefore, there is clear medical evidence, as reflected in the SmPC, that altering the eculizumab dosing regimen will cause serious and potentially life-threatening complications in aHUS patients.

As described throughout our September submission, aHUS is a life threatening, progressive genetic disease. The severity of the disease is apparent in the pre-eculizumab era, as it has been reported 33% to 40% of aHUS patients die or progress to ESRF with the first clinical manifestation in the international TTP/HUS registry analysis with all available supportive care, including PE/PI, prior to the availability of eculizumab.(Caprioli et al, 2006, Noris et al 2010) Taylor et al 2009 also cite poor outcomes in patients receiving plasma exchange/plasma infusion (PE/PI) as supportive care, with an initial mortality of 25% and 50% renal failure rate in surviving patients. Recent medical evidence from TMA registries (Coppo et al 2010 and Hovinga et al 2010) report a mortality of 13% (mean 17.8 months) and 32% mortality (median 4.4 years), respectively, demonstrating a continued mortality in aHUS patients with supportive care over a median of 4.4 years.

Patients with aHUS have one or more genetic mutations (although the mutation(s) are frequently not identifiable), causing life-long deficiency in complement inhibitors or regulators. Loss of complement regulators on endothelial cells and platelets leads to chronic uncontrolled complement activity causing on-going platelet, endothelial, and white blood cell activation and subsequently chronic inflammation and thromboses (blood clots) in small blood vessels throughout the body, a process known as systemic TMA.(Noris and Remuzzi, 2009; Karpman et al, 2006; Stahl et al, 2008; Stahl et al, 2011) Several in vitro and in vivo studies demonstrate that loss of complement regulation increases complement deposition on endothelial cells and platelets resulting in more severe endothelial injury, severe glomerular deposition of fibrin and platelets,

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increased loss of glomerular endothelial cells, and greater impairment of renal function compared to cells with sufficient complement regulation.(Hughes 2000; Turnberg 2003; Bao 2010; Heinen et al 2013) This on-going, ever-present uncontrolled complement activation, provides a constant and life-long threat to patients. As seen with patients in the C08-003 trial, a continued decline in renal function was seen over time prior to eculizumab treatment.(Legendre et al 2013) At any moment, aHUS patients are additionally vulnerable to sudden, severe, devastating, and irreversible TMA with loss of a vital organ including the brain, heart, gastrointestinal system, and/or kidney. Further, this on-going organ damage occurs despite use of PE/PI and stable platelet counts.(Legendre et al 2013) The on-going clinical deterioration even with PE/PI is explained because PE/PI is ineffective at adequately controlling the on-going systemic complement activation in patients with aHUS. On-going and elevated complement activity (approximately four-fold higher than in normal patients) occurs in aHUS patients receiving PI.(Heinen et al 2013) Conversely, eculizumab completely blocked complement activity to normal levels.(Heinen et al 2013) The eculizumab clinical trials demonstrate that long-term treatment with eculizumab, and thus a complete block of uncontrolled complement activity, significantly improved renal function (estimated Glomerular Filtration Rate (eGFR) ≥15 ml/min/1.73m^2) and reduced/eliminated proteinuria (representing on-going kidney damage) in 40% of patients over 1 to 2 years of chronic treatment, which is consistent with the observed long-term chronic inhibition of complement activation in patients with aHUS properly dosed with chronic eculizumab treatment.

Published case reports have shown that a reduced dose or discontinuation of eculizumab may lead to rapid deterioration in organ function. In several of these reported cases re-initiation of eculizumab therapy following discontinuation could not be counted on to salvage organ function.(Mache et al, 2009; Vilalta et al, 2012; Zuber et al, 2011; Chatelet et al, 2009) Not only are patients who discontinue at high risk for severe TMA complications, they also forego the on-going clinical improvement observed with on-going ECU treatment in the long-term follow-up studies. Long-term efficacy data from the prospective clinical trials show on-going improvement in haematological and renal outcomes for patients remaining on eculizumab treatment.

12. **Priority question:** Please provide full details as to why patients chose not to enter into the extension phases of the trials.

Alexion Response:
Clinical trial investigators and patients were not required to provide reasons for not continuing in the extension study. However, a summary of the responses that were shared is provided below for the following studies: C08-002, C08-003, C10-003, and C10-004.

C08-002: [redacted]

C08-003: [redacted].

C10-003: [redacted].

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C10-004: [redacted]

13. The search strategy provided in Table C1 on Page 60 of the submission does not match with the search strategy provided in Appendix 17.1.4 pages 219-220. Please clarify which search was used to identify the clinical evidence.

    Alexion Response:
    Table C1 contains the correct search terms used to identify clinical evidence. Additional search terms provided in Appendix 17.1.4 were mistakenly added and do not accurately depict the search strategy. However, the additional search strategy details provided in Appendix 17.1.4 are correct and relevant to the search defined in Table C1 as well as the search results reported in section 9.3.1 of Appendix G in our September 2013 submission.

14. On page 218 of the submission, the date of the searches ranges from 1947 to 4 July 2013; however, the search strategy provided on page 220 suggests date and language restrictions e.g. limited to human, English Language and yr="2000-Current". Please clarify the dates of the clinical searches and justify language restrictions.

    Alexion Response:
    The date limitation of 2000-current was used to ensure that only current and relevant information would be assessed, considering the evolving nomenclature and understanding of aHUS and other TMA related diseases. English language limitation was used to identify the publications most likely to be relevant to the English setting.

15. Please provide details of the searches used for non-RCT evidence. On Page 220, the submission states that *"Due to the difficulty in identifying a reliable search strategy, and the lack of high level evidence in the form of randomised controlled trials, the term 'trial' was extended to include case series, retrospective trials, registries, cohort and case studies";* however, no details of the search strategy are included.

    Alexion Response:
    Due to the limited availability of randomised controlled trials (RCT) evidence, the search described for RCT evidence was expanded for non-RCT evidence to include the terms as described case series, retrospective trials, registries, cohort and case studies. Other details of the non-RCT search (search terms, databases, date, and language limitations) were conducted for the RCT evidence search.

16. Was Medline (R) In-Process searched? If not please provide justification for not searching Medline (R) In-Process (page 59 and 218)?

    Alexion Response:
    MEDLINE In-process database was not individually searched. Embase was utilised for the search, which includes In-Process citations in its database.

17. Given the limited evidence relating to the safety and efficacy of eculizumab, please explain and justify the decision to exclude case series from the systematic review.

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Alexion Response:
Although case series were identified as relevant published studies (Table C4), these 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.

18. Section 9.5 - Please explain why an RCT appraisal tool has been used to critically appraise the non-randomised studies of eculizumab.

Alexion Response:
No RCTs were identified for appraisal. In Section 9.5, the NICE guideline template provided a table for critical appraisal of RCTs and for observational studies. An alternative template for non-RCTs was not identified that would provide a similar appraisal as the one requested in the included RCT template.

19. Table C8 – Please clarify how "PE/PI sessions during current aHUS event, Median (min; max)" have been calculated.

Alexion Response:
In the C08-002 and C08-003 studies, the pre-eculizumab treatment period was from the later of (1) the start of the current aHUS episode or (2) eight weeks prior to the first eculizumab dose until the first eculizumab dose.

In the C10-003 and C10-004 studies, the pretreatment observation period was from the later of (1) the start of the current aHUS episode or (2) eight weeks prior to the first eculizumab dose until the first eculizumab dose.

20. How were patients diagnosed with confirmed aHUS within studies C08-002, C08-003, C09-001r, C10-003 and C10-004?

Alexion Response:
In the prospective C08-002, C08-003, and C10-004 studies, as well as the C09-001r studies, the diagnosis of aHUS was aligned with clinical practice. A clinical diagnosis of aHUS was confirmed in the clinical trials based on evidence of low platelet count (or maintained platelet counts in C08-003 while on PE/PI), evidence of microangiopathic haemolysis (LDH ≥1.5 upper limit of normal (ULN) range), impaired renal function (increased creatinine above ULN), ADAMTS13 >5%, and no positive result for STEC infection.

In the prospective paediatric C10-003 study, patients had to have a platelet count < lower limit of normal (LLN) range at screening and baseline, exhibit signs or symptoms of haemolysis at the start of current aHUS event (i.e., LDH ≥1.5 ULN and haemoglobin ≤ LLN), and a serum creatinine level ≥97 percentile for age at screening (patients requiring dialysis for acute renal failure were also eligible). All patients demonstrated ADAMTS13 activity >5%, consistent with the adult (C10-004) trials, and an aHUS diagnosis.

There was no requirement of identified genetic mutation to confirm diagnosis of aHUS in any of the trials, consistent with standard medical practice. All patients demonstrated an objective improvement in complement activation with eculizumab treatment, and clinical improvement was observed with eculizumab, validating the aHUS diagnosis.

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21. Does the age range of patients in studies C08-002, C08-003, C09-001r, C10-003 and C10-004 reflect the age range of patients in UK clinical practice? Please provide evidence to support your response.

Alexion Response:
The age range of patients in England currently diagnosed with aHUS, and requiring treatment with eculizumab, is broad and reflective of the patient groups studied in the trials stated in the question above.

A renal unit survey conducted in 2010 determined that, at that time, there were 139 confirmed cases of aHUS in the UK of which 43 were paediatric cases and 96 were adult. Alexion does not have a breakdown of specific ages for patients included in the renal unit survey.

Since the launch of eculizumab for the treatment of aHUS in England, and the subsequent release of the recent NHS England "Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome," Alexion is aware of patients of all ages either initiating eculizumab therapy or being deemed eligible pending transplant availability. Thus, for patients in England, the broad age ranges investigated in the eculizumab studies are consistent with current clinical practice.

A breakdown of the age categories studied is shown below:

Trial	N (ITT)	Age (years), Median (min; max)	Age Category			
			Infant (<2 years)	Children (≥2-12)	Adolescent (≥12-≤18)	Adult (≥18)
C08-002	17	28 (17; 68)	0	0	1	16
C08-003	20	28 (13; 63)	0	0	5	23
C09-001r	30	12 (0.17; 51.4)	5	10	4	11
C10-003	22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C10-004	41	[redacted]	0	0	0	41

22. Does the baseline eGFR status of patients in prospective studies C08-002, C08-003 reflect the current mix of aHUS patients in England and Wales? Please provide evidence to support your response.

Alexion Response:
Alexion is not clear why this clarification question refers to patients in Wales given the remit of this evaluation is specific to NICE in England. Therefore, our response below is specific to patients in England.

The baseline eGFR in studies C08-002 and C08-003 are generally representative of patients with aHUS given that the specific inclusion criterion relating to kidney function was serum creatinine greater than upper limit of normal (ULN) across both studies. In this respect, there was no restriction in terms of eGFR status and patients were enrolled across a range of eGFR values. In addition, no patients were excluded from the studies on the basis of eGFR status.

In terms of specific patients requiring eculizumab therapy currently in England, Alexion does not have access to the clinical parameters of these patients if they were not

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involved in the clinical studies. Therefore, we cannot provide data to support a response to NICE's question. A survey of all treating physicians across England would be necessary to collect such data which, given the timeframe and ethical considerations, this was not feasible.

23. Are there any data available for transplant failure rates in those patients with prior kidney transplants (Section 9.4.4, page 85)?

Alexion Response:
There was one patient in the prospective clinical trials (C08-003; [redacted]) who received a kidney transplant while receiving eculizumab during the maintenance period. That patient experienced no severe TMA complications/aHUS occurrence in the allograft throughout participation in the clinical trial [redacted].

In the retrospective data collection study (C09-001r), one patient (Patient 110-007), received eculizumab beginning 10 days after a kidney transplant to prevent aHUS in the allograft. This patient experienced no severe TMA complications/aHUS occurrence in the allograft function and received eculizumab throughout participation in the study (last reported follow up of greater than one year).(Zimmerhackl et al, 2010)

24. Section 9.4.4. Page 85 - for the primary endpoint of reduction in TMA, what is the threshold whereby a reduction is clinically meaningful?

Alexion Response:
aHUS is characterized by uncontrolled complement activation and subsequent TMA, haemolytic anaemia (measured as an increase in LDH), and end-organ damage including kidney failure despite use of SOC including PE/PI. This on-going clinical deterioration in aHUS patients (with or without use of PE/PI) is explained because PE/PI is ineffective at adequately controlling the on-going systemic complement activation in patients with aHUS. Patients with aHUS have on-going and elevated complement activity (approximately four-fold higher than normal patients) even when receiving SOC.(Heinen et al 2013) Long-term chronic inhibition of complement activation in patients with aHUS properly dosed with chronic eculizumab treatment is the clinical goal of treatment.

In the prospective C10-003 and C10-004 clinical trials, the primary endpoint was complete TMA response (a modified TMA response in C10-004 to match C10-003), defined as haematologic normalisation based on platelet count and LDH, and ≥25% improvement in serum creatinine from baseline, confirmed by two consecutive measurements obtained at least four weeks apart. This primary endpoint is a very high response hurdle as its achievement includes both haematological evidence of TMA and improved end-organ function in an extremely short period of time.

Although the regulatory end point achieves this high hurdle, such criteria should not be used to define the threshold for meaningful clinical benefit since the fundamental defect in aHUS patients is complement dysregulation—which has been shown to cause all subsequent morbidities and premature mortality. The improvement in end-organ function due to inhibiting complement activity can take time as demonstrated in the C08-003 trial where some patients required more than one year to experience improvement in end-organ function. Based on the progressive nature of aHUS, it is expected that 65% of patients will progress to permanent renal impairment, ESRF, or dialysis or die within

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one year of clinical manifestation of aHUS. Because of the on-going complement activation in patients with aHUS, irrespective of supportive care, stability of organ function itself is also a clinically meaningful benefit in these patients.

As stated above, due to the on-going complement activation in all aHUS patients, and the fact that the fundamental defect in aHUS patients is complement dysregulation—which has been shown to cause all subsequent morbidities and premature mortality—reduction in complement activation is a clinically meaningful outcome. The level of this response is extremely high by the standard of pharmaceutical interventions with 100% of patients achieving substantial complement inhibition with eculizumab treatment in pivotal trials. [redacted].

25. Section 9.7 - Are the adverse event data presented in Table C12 and C13 at 26 weeks or for the duration of the study (64 weeks)?

Alexion Response:
The data presented are for the duration of the study (64 weeks).

26. Were responder rules employed in prospective studies C08-002, C08-003, C10-003 and C10-004?

Alexion Response:
Responders were defined by the primary end point of the respective clinical trial as specified in the protocol. Once a responder was identified, the patient was considered a responder.

27. During the previous appraisal of eculizumab, study C09-001r included 15 paediatric only patients. This study now includes 30 patients in the manufacturer's submission. How were the additional 15 patients chosen for the retrospective study?

Alexion Response:
Alexion is surprised that a previous appraisal of eculizumab is being cited here since during our scoping meeting, NICE was clear that our most recent submission should be seen as "stand-alone" and not referenced to other submissions made in England to the Advisory Group for National Specialized Services (AGNSS) or the Clinical Priorities Advisory Group (CPAG). That said, we provide clarity below regarding the patients including in the retrospective C090-001 study.

As described in the response to Question 4 above, Alexion was able to identify 36 patients who were diagnosed with aHUS and treated with eculizumab outside the two Alexion-sponsored controlled clinical trials, C08-002 and C08-003. Data were compiled retrospectively for aHUS patients undergoing treatment with eculizumab in an uncontrolled clinical setting. Of the 36 patients identified, 30 patients agreed to participate, 15 of which were paediatric patients under 12 years of age. During regulatory submission to EMA, a sub-analysis of paediatric patients was provided to provide efficacy and safety of eculizumab in paediatric patients.

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28. Page 28 states that study C08-002 includes short-duration patients and study C08-003 includes long-duration aHUS patients. However, page 70 states that study C08-002 is in patients who were newly diagnosed, had an existing diagnosis or were post-transplant. The same inclusion criterion was used in study C08-003 (see page 73). Please clarify the patient populations in these studies.

    Alexion Response:
    In the C08-002 study, the screening period for this study was a maximum of three days. Patients who met all of the Inclusion Criteria and none of the Exclusion Criteria were immediately enrolled into the Treatment Period. This led to the inclusion of patients with a short duration of their aHUS clinical manifestation. In the C08-003 study, the Screening Period (Visit 1) for this study was longer—a maximum of two weeks. Patients who met the plasma therapy (PT) requirements at the Screening Period were enrolled in an eight-week Observation Period to observe clinical laboratory testing, platelet counts, haemolytic markers, pro-thrombotic measures, pro-inflammatory markers, and complement markers. These measures, and samples for renal function measures, were collected on a weekly basis. During the Observation Period, each patient was observed to receive at least one PT session every two weeks and no more than three PT sessions per week (at an unchanged frequency) for at least eight weeks before the first dose of eculizumab. Due to the eight-week Observation Period, and lower use of PE/PI, these patients tend to have a longer duration of aHUS.

Section B: Clarification on data relating to the cost model and value for money

29. **Priority question:** The submission states that aHUS affects both adults and children and some of the clinical trial evidence includes paediatric patients. However, the economic analysis relates to a single cohort aged 28 years and does not include younger patients. Please explain why no analysis has been undertaken for children.

    Alexion Response:
    Our target patient population was intended to capture all patients for which eculizumab for aHUS is indicated, including adults and children. We use age 28 as an average age for the entire cohort, which is comprised of five weight intervals; [redacted] of patients are adults weighing over 60 kg, while the other modelled patients are children distributed across the four other weight intervals.

    We describe how children specifically are included in the model in multiple instances. For example, we describe this input in “Table D4: Summary of variables applied in the cost-consequences model” (pages 156-157 of our September 2013 submission); see for example, “Table D7: Patient weight by age”. We describe how we use UK-specific data to model aging and weight gain among the children. In the electronic (Excel spreadsheet) version of the model, the header “Patient weight intervals at baseline,” allows the user to input the baseline distribution of patients by weight interval, with four paediatric weight intervals.

    Please note that the bias in the model due to this approach is small, and “works against” eculizumab. In the model, children face the background death rate of a 28-year old patient at baseline; similarly, those who are older than age 28 live longer in the model by also having the background death rate of a 28-year old at baseline.

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30. **Priority question:** Please explain why the model only uses data from studies C08-002 and C08-003. Specifically, given the paucity of evidence relating to eculizumab, why were interim data from studies C10-003 and C10-004 not also used to inform the economic analysis?

    Alexion Response:
    At the time of the economic model development, data from the C10-003 and C10-004 studies were not available for incorporation into the model. Initial results from the C10-003 and C10-004 interim analyses were included in our September 2013 submission, even though it was not feasible in the short timeline required by NICE to incorporate the data into the economic model as well.

31. **Priority question:** The ERG has concerns about the calculation of transition matrices for eculizumab. Specifically, please explain how it is mathematically appropriate to observe time-dependent matrices and then weight these by sample size to derive time-independent matrices?

    Alexion Response:
    Our model of eculizumab efficacy is equivalent to deriving a Markov matrix by estimating an ordinal probit, where the dependent variable is patient i's chronic kidney disease (CKD) stage in the future time period (t+1), and where the independent variables are patient i's CKD stage in the current time period (t), using an unbalanced panel. However, it is more transparent for NICE's review for us to estimate the model in the way we did.

    Also, we would note that our estimation is not time dependent. We did not assume that the time relative to baseline in the trials has an independent effect on future CKD stage, which is equivalent to the memoryless Markov assumption.

32. **Priority question:** The standard care transition probabilities are based on the results of the LOWESS regression of the pre-treatment phase in the C08-002 and C08-003 studies. This regression uses the rate of change in eGFR per day to derive 6-monthly transition probabilities. The estimated rate of change was -0.03 points/day which according to the submission, given a 15-point interval in each CKD band, leads to a transition probability of 0.367 (calculated as [0.03 x 182.5]/15). The ERG believes that this is mathematically incorrect – if the rate had been -0.10 or higher this would lead to a probability which is greater than 1.0. Please consider which approach is most appropriate and provide justification for your choice, or updated analyses (if a different approach is adopted).

    Alexion Response:
    We did not use LOWESS regression to estimate the standard care transition probabilities; we used a fixed effects specification of a linear panel model (using the *xtreg* procedure in STATA v.13) regressing eGFR on days in the pretreatment period. The LOWESS regression was estimated to assess the assumption that the effect of eGFR on pretreatment days was linear. This is evident by the header on page 142 of our submission describing LOWESS ("Testing the linearity assumption: Is it reasonable to assume SOC treated patients would continue to get worse?").

    It is true that we are mapping continuous eGFR into multinomial (ordinal) space per our calculation, and that if the effect were sufficiently large (or small), it could violate the

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boundedness of the multinomial (or probability [0,1]) space we are mapping into. However, the regression specification indicates that a coefficient (i.e., rate) of 0.030 was estimated with a "tight" confidence interval—the standard error was 0.003. The 95% confidence intervals around the coefficient were 0.024 and 0.036, translating into 95% confidence intervals around the transitional probabilities of 30.5% and 42.6%. 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. Future research could employ more sophisticated non-linear ordinal models to do the mapping, but would sacrifice the transparency of our approach, and would not lead to different results.

33. **Priority question:** Please explain why the probability of receiving a transplant for patients receiving eculizumab is zero - this was non-zero in versions of the model considered in the previous appraisal.

Alexion Response:
As noted above, Alexion is again surprised that a previous appraisal of eculizumab is being cited here since NICE was clear that our most recent submission should be seen as "stand-alone" and not referenced to other submissions made in England. However, in the interest of full transparency, we provide additional clarification below.

The most recent version of the economic model provided to NICE represents the most comprehensive assessment of the benefits and costs of eculizumab in aHUS that have been undertaken by Alexion for the purposes of conducting a UK health technology assessment. Alexion has refined previous versions of the model based upon up-to-date data, further expert involvement, and feedback received during other assessment processes. We believe that our latest submission to NICE should be appraised on its own merits and not relative to previous submissions to different agencies, particularly as new data become available and are incorporated into the model.

It is true that eculizumab may make aHUS patients candidates for transplant when they otherwise would not have been a candidate prior to use of eculizumab since patients receiving SOC have a high probability of graft failure. However, the data from the Alexion clinical trials indicate that liver function is improved for the majority of patients so that transplantation is no longer needed. There was only one transplant in the C08 trials data; compared to the pretreatment period, the transplant rate declined substantially. Specifically, in the pretreatment period, there were (352*37) days of observation time, and 25 transplants were recorded in 16 patients.

Our current model submitted to NICE in September 2013 handles transplant the same way as the revised March 2012 AGNSS version of the model. This is explained in the section of our most recent submission entitled: "Transplant Rates for Eculizumab" on page 138. Please also note that the results of the C08-002 and 003 studies were published in the *New England Journal of Medicine* (Legendre et al, 2013); only one transplant is reported therein. [redacted].

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34. **Priority question:** Please explain why the cost of eculizumab in the model includes dose reductions (and hence lower costs for eculizumab) for paediatric patients when the model cohort enters the model at age 28 years.

    Alexion Response:
    Please see our answer to Question 29 above. We model the distribution of patients expected to receive eculizumab in the UK, assuming an average age based on the C08 studies.

35. **Priority question:** Please explain why HRQoL for each state is valued 0.208 lower for standard care compared to eculizumab. What is this utility loss intended to represent? Please clarify the evidence available to support this.

    Alexion Response:
    The 0.208 is the gain in HRQOL from eculizumab therapy at 64 weeks versus baseline, taken from Legendre et al, 2013.

    In Legendre et al. 2013, at the end of Table 2, the mean change in European Quality of Life Group 5 Dimensions Self-Report Questionnaire (EQ-5D) is presented for the two trials. The increment for all patients is 0.208 over the 64-week period, based on the weighted average calculation in Table D13, "Measurement of eculizumab health utility increase over SOC." Note that though this is over a 64-week period, the results are similar by week 26 (0.201) in the Legendre publication, and in fact, the effect is evident before the end of month three in the C08-003 trial and before the end of month one in the 002 trial (see figures in answer to question 53), and we assume that this effect occurs within six months on eculizumab and persists in the model. In the base case analysis, we assume that every patient alive gets the increment evenly across the disease states. We test this input in the sensitivity analysis.

    During interviews with experts in support of this submission, the participants were asked to explain what factors drove the improvement in EQ-5D quality of life scores over the duration of the clinical trials. All five experts attributed this improvement to the absence of the need to undergo plasma exchange therapy. The experts emphasised the great burden that PE places on patients, physically, psychologically, and by restricting their ability to live normal lives. This burden is described in detail in Section 7.1 of our September submission.

36. **Priority question:** Why were the adverse events associated with eculizumab (Section 9.7 of the submission) excluded from the model?

    Alexion Response:
    As described in Section 12.2.4 of our initial submission, the adverse event (AE) profile for eculizumab is overall mild and eculizumab is well tolerated. Adverse reactions were mostly mild to moderate in severity. The most commonly reported AEs from the two main eculizumab trials were headache, dizziness, nausea, and pyrexia, each occurring in 5% or more patients. Although almost all patients reported AEs in the aHUS studies, few were considered drug-related by the investigators. Specifically, in the two prospective aHUS studies, only one AE led to treatment discontinuation, and this AE was deemed unrelated to study drug.

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

Finally, AEs related to the background disease have also never been measured in a high-quality registry or clinical trial setting. One expert hypothesized that there may be micro-TMAs experienced by patients with complement disorder, if there underlying disease is untreated, that reduces quality of life. To adequately identify the causal effect of eculizumab versus SOC on AEs, the background rate would also have to be measured, but it is not.

Because of the generally mild AEs associated with eculizumab, and the fact no specific source exists measuring AE rates for SOC or related to the aHUS background rate, the model does not include any health or cost implications for treatment-related AEs.

Because of the generally mild AEs associated with eculizumab, and the fact no specific trials source exists for any of the SOC methods evaluated, the model does not include any health or cost implications for treatment-related AEs.

37. **Priority question:** Reasons for patient discontinuation within studies C08-002 and C08-003 are given on Page 86 of the submission. Please provide the patient number for each of these patients so that they can be identified in the “Ecu_trials_data” worksheet in the submitted model. E.g. patient number 2-029-001. Please provide the patient number for the following patient discontinuations:

    a. CO8-002 - Protocol violation: patient diagnosed with SLE approximately one week after the first dose of eculizumab

    b. CO8-002 - Discontinued due to an adverse event deemed not related to study drug

    c. CO8-002 - Completed treatment period, and the investigator elected not to enrol patient in extension period

    d. CO8-002 - Completed treatment period, and investigator elected not to enrol patient in extension period. Data were not collected during follow-up period as patient refused to continue participation

    e. CO8-002 - Adverse event (“decrease in renal function” per investigator) deemed not related to study drug (during extension study)

    f. CO8-002 - Adverse event (worsening of renal function) deemed not related to study drug (during extension study)

    g. C08-003 – Patient who completed the 26 week study period who did not continue to the extension study period due to personal reasons

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h. C08-003 – Discontinued during the extension study period due to an AE deemed not related to the study drug

Alexion Response:
This is an unusual request from a health technology assessment agency—to ask for specific personal identifiers for patients experiencing AEs. Based on concerns about patient confidentiality, we do not feel comfortable disclosing these patient ID numbers. We have provided NICE with patient-time observations for CKD status at 6-month intervals; however, no individual patient is identifiable in the trials from this information (e.g., specific information on timing of last observations is not provided). Alternatively, NICE's current request for specific personal identifiers for patients experiencing AEs could lead to identification of unique patients and could violate confidentiality agreements with trial patients.

Please note that in line with the SmPC, Alexion strongly advises against discontinuation of eculizumab in aHUS patients due to the chronic nature of the disease, and the continuous risk of sudden, life-threatening events. We advise patients and their physicians that while it is tempting to view apparent improvement of health as a basis for discontinuation, aHUS is a chronic, lifelong disease which places the patient at on-going risk of life-threatening medical events if treatment is discontinued.

38. **Priority question:** Page 18 includes estimates of losses in productivity, government benefits and tax revenues. Please provide the underlying calculations, evidence sources and assumptions used to produce these estimates.

Alexion Response:
As noted on page 18 in our initial submission, Section 14.2 contains the details of the calculations related to losses in productivity, government benefits, and tax revenues. Specifically, the calculations, evidence sources, and assumptions used to produce the estimates are outlined in Pages 191 and 192 of our original submission and are summarised in Table E1, which is included below for reference.

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Table E1: Estimated government (non-NHS) and societal costs associated with aHUS and potential savings with eculizumab

Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Patient lost productivity	40% of adult aHUS patients were out of work in UK aHUS patient survey (Section 7). 23% of out of work adult aHUS patients were retired. Therefore estimate that 27% (0.4 x 0.67) of all adult aHUS patients are out of work vs. 7% for general population. Assume 20% excess unemployment rate. Assume adults represent 50% of total population	Average median UK annual earnings £26,500 (ONS 2012)	0.2 x 0.5 x £26,500 = £2,650	£784,400	£588,300	£196,100
Carer lost productivity (current carers)	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) Carers on average lost 18 hours of paid work per week, which represents 46% of an average 39 hour working week (ONS 2012)	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.54 x 0.82 x 0.46 = £5,397	£1,597,729	£1,198,297	£399,432

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Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Carer lost productivity (ex-carers)	The household income of ex-carers is approximately half of household income of general population (McLaughlin and Ritchie 1994). Assumes ex-carers = 25% current patients (82% were informal carers (UK aHUS patient survey))	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.5 x 0.25 x 0.82 = £2,716	£804,010	£603,008	£201,003
Patient receipt of government benefits	Assume 25% of aHUS patients receives benefits	High-medium need total weekly benefits = £235 (Wood 2010)	0.25 x £235 x 52 = £3,055	£904,280	£678,210	£226,070
Carer receipt of government benefits	54% of patients, regardless of age, have a carer, 82% were informal carers (UK aHUS patient survey) 61% of carers receive Carer's Allowance (Carers UK, 2007)	Carer's allowance = £59.75 per week (UK Government 2013)	0.54 x 0.82 x 0.61 x £59.75 x 52 = £839	£248,411	£186,308	£62,102
Lost tax revenues for patients	20% excess employment rate for patients (see above) Average percentage of income that goes on tax = 17.8% (LSE 2013)	Average median UK annual earnings £26,500 (ONS 2012)	0.2 x £26,500 x 0.178 = £943	£279,246	£209,434	£69,812

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Item	Quantity	Unit cost	Total annual saving (cost) per carer/ patient	Total annual saving (cost) across 296 aHUS pts	Total annual saving (cost) assuming: 75% improvement after eculizumab	Total annual saving (cost) assuming: 25% improvement after eculizumab
Lost tax revenues for carers	54% of patients have a carer (82% were informal carers) who lose 18 hours work per week on average (see above) which represents 46% of an average 39 hour working week (ONS 2012) Average percentage of income that goes on tax = 17.8% (LSE 2013)	Average median UK annual earnings £26,500 (ONS 2012)	£26,500 x 0.54 x 0.82 x 0.46 x 0.178 = £960	£284,396	£213,297	£71,098

Table Sources:

- Office of National Statistics (ONS). Patterns of Pay: Results from the Annual Survey of Hours and Earnings, 1997 to 2012. Available at: www.ons.gov.uk/ons/dcp171766_300035.pdf. Accessed 6 September 2013.
- Wood C & Grant E. Counting the Cost, London: Demos 2010. Available at www.demos.co.uk.
- UK Government. 2013. Carer's Allowance. Available at: https://www.gov.uk/carers-allowance/overview. Accessed 6 September 2013.

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39. Table D2 page 135 - In the economic analysis, costs and outcomes are discounted at a rate of 1.5%. Please explain why the discount rate of 3.5%, as stipulated in the NICE Reference Case was not used.

Alexion Response:
In the NICE 2013 Guide to the methods of technology appraisal 2013 (section 6.2.19) it states the following:

> "In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. 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. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."

Alexion believes that eculizumab for the treatment of aHUS meets the criteria outlined above, as described in the table below:

Criterion	Eculizumab in aHUS
In cases when treatment restores ***people who would otherwise die or have a very severely impaired life to full or near full health***	From Section 6.1 of eculizumab submission: The disease affects both children and adults and has a very poor prognosis, demonstrated by the fact that 33% to 40% of aHUS patients die or progress to end-stage renal failure (ESRF) requiring dialysis with the first clinical manifestation.(Caprioli et al, 2006; Noris et al, 2010) The chronic nature of aHUS results in progressive, on-going morbidity as 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on plasma exchange or plasma infusion (PE/PI) or dialysis and a progressive increased mortality rate thereafter. Long-term data have shown a mortality rate of 32% at 4.4 years median follow-up.(Hovinga et al, 2010)
In cases when ***treatment restores people*** *who would otherwise die or have a very severely impaired life to full or near full health*	From Section 9.6 and 9.9 of eculizumab submission: Eculizumab is designed to block activation of the terminal stage of the complement system directly and potently.(Rother et al, 2007) As a result, use of eculizumab reduces the underlying systemic complement-mediated TMA process and subsequently can reverse or prevent further kidney damage, which has been shown to lead to a discontinuation or avoidance of dialysis. Eculizumab has also been shown to prevent progression of other organ damage in aHUS patients, and has demonstrated a reduction or elimination in the need for PE/PI as well as a significant improvement in patients' quality of life.(Legendre et al, 2010; Muus P et al, 2010; Licht et al, 2011; Greenbaum et al, 2011; Alexion, 2012; Legendre et al, 2013)
when this is sustained over a very long period (normally at least 30 years)	From Section 12.2.6 of eculizumab submission: The mean age of patients in the economic analysis was 28, based upon the average age of patients at baseline in prospective trials C08-002 and C08-003. In the base case economic analysis 84.7% of patients were still alive after 30 years post treatment initiation.

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Criterion	Eculizumab in aHUS
it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved	While long-term data is not yet available, the long-term health benefit derived from eculizumab is supported by the extent to which eculizumab controls the underlying disease, as well as the survival data from the clinical trials (at 3 years). Eculizumab has been demonstrated to block activation of the complement system directly and potently, thus limiting the underlying systemic complement-mediated TMA process (Rother et al, 2007). In eculizumab clinical trials, haematologic normalisation was achieved by 76% of patients (95% CI: 50-93%) and in up to 90% of the 10 patients with both abnormal platelet count and LDH at entry. The duration of response continues into the extension phase, with a median duration of response limited only by the current data cut-off and is currently 258 days (range 196-431) for haematologic normalisation and 267 days (range 217-389) for complete TMA response. Importantly, patients demonstrate stable or improved organ function (reduction or stabilization in eGFR and proteinuria), some patients demonstrating benefit after one year of chronic eculizumab treatment. In the eculizumab clinical trials there was one death observed in the C08-002 and C08-003 trials extension data (using the three-year extension data) in a patient population that was expected to progress to ESRD and early mortality. The death was determined not to be related to the study drug. The one event occurred over 176.1 six-month intervals, yielding a six-month death rate of 0.57%. (Eculizumab submission Section 12.1.7)
Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs	It is highly unlikely that the NHS could be exposed to significant irrecoverable costs for the following reasons: 1) NICE will review the appraisal decision after 2 years and subsequently; and 2) The patient population affected by aHUS is very small and the predicted budget impact is less than £20m at 2 years post-NICE decision. In addition, it is anticipated that specific centre/s of expertise will be commissioned to ensure appropriate use of eculizumab in correctly diagnosed aHUS patients across England. This is currently the case with all suspected cases of aHUS being referred to the centre in Newcastle where diagnosis is confirmed and treatment with eculizumab recommended where appropriate. This will mitigate the risk of eculizumab being prescribed for inappropriate cases. Patients on eculizumab will be monitored regularly by the centre/s of expertise to ensure optimal on-going management. The fact that there is a relatively small amount of money under discussion, and a process by which the return on this investment can be closely monitored, will significantly mitigate the risk of irrecoverable investment.

40. Section 9.8.1 states the following: *"Studies C08-003 and C08-002, described in detail within this submission, enrolled patients with different clinical characteristics. Study C08-003 included patients with long duration of aHUS, prolonged PE/PI exposure and*

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substantial kidney damage, whereas C08-002 included patients with progressing TMA and shorter disease duration. These trials demonstrated the efficacy of eculizumab in a broad range of aHUS patients, reflective of the addressable population. However, this does not lend itself to meta-analysis and would not provide results which are more informative than those included within the submission document. Due to the lack of RCTs and the heterogeneity of patients included in the non-randomised prospective and observational trials included in this submission, evidence synthesis or meta-analysis were not performed."

Please comment on validity of pooling patient-level data from studies C08-002 and C08-003 in the model to estimate CKD transition probabilities.

Alexion Response:
The base case was designed to describe the set of patients with aHUS indicated for eculizumab treatment. This implied pooling the C08-002 and 003 patients. We also performed sensitivity analysis by looking at each trial (i.e., patient group) separately.

a. Please explain why the rate of eGFR change was used rather than calculating the CKD state at the beginning and end of the pre-treatment period and adjusting for observation time.

Alexion Response:
Mathematically, working with a continuous dependent variable requires fewer assumptions and allows for more modelling options than a multinomial/ordinal variable. Since CKD stage is determined by eGFR, there is no loss from using eGFR and mapping to CKD stage. "Adjusting for observation time" for a multinomial/ordinal variable is less straightforward than doing so with a linear regression. Ultimately, our approach is more flexible and transparent.

b. Please explain why data from the pre-treatment period were used rather than published studies e.g. Noris et al 2010 or Hovinga et al 2010.

Alexion Response:
The March 2012 questions Alexion received from the TAR group indicated that the AGNSS reviewers were unclear as to why Hovinga was used to describe outcomes, namely mortality, for SOC-treated patients. We have continued to use these cohorts as the basis of what a SOC-treated patient population with aHUS would be. However, proximal outcomes, like transitions between CKD stages and ESRF, are also important in aHUS. In the AGNSS submission, non-mortality SOC outcomes were based only on expert opinion, given that there was not time to consider options to use data for these outcomes. We revisited parameterizing these proximal outcomes in our current model, given that we had additional, albeit limited, time to prepare the most recent submission to NICE.

The pre-treatment period in C08-002 and 003 was an appropriate set of available data with which to model SOC, given that the selection of patients was identical to the treatment period in the trials and the patients received SOC in the pretreatment period, including PE/PI and dialysis. The outcomes in the pretreatment period are reported In Legendre et al. In the section of our most recent September 2013 submission to NICE entitled "SOC: Transitions between CKD States" on page 139-140 we state:

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

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

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

c. Please suggest more plausible values for these quantities.

Alexion Response:
Per an email from NICE on October 16, 2013, it was suggested that we focus our response on Questions 40a and 40b as there was some confusion from the ERG regarding what exactly was meant in Question 40c by the phrase "plausible values for these quantities".

If "quantities" refers to the rate of eGFR over time, we describe the linear model and linearity check in the section entitled "Data and Methods - Analysis of relationship between eGFR and days using pre-treatment data" on page 140-144 of our September 2013 submission. Please also see the answer to Question 32 above for more detail.

Overall, we believe all of the quantities used in the model are plausible, to the extent that there are data available describing an ultra-rare disease like aHUS. If NICE has evidence to the contrary, we would enjoy and appreciate the opportunity to work through the data and methods together.

41. Please explain how the model deals with competing risks of events (e.g. mortality and disease progression).

Alexion Response:
The Markov traces are computed based on the Markov matrix. State transition probabilities from a given state (including the probability of returning to that state) sum to one. The derivation of each probability is described in the section entitled "Standard of Care (SOC) Arm Transitions" on pages 139-146 of our September 2013 submission. The CKD transition data come directly from the trials. The mortality transitions come from three sources, CKD 5, excess non-renal mortality and background mortality. Background mortality is fixed for a given five year band; other transitional probabilities

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are derived from the space (1 - background mortality); as such, background mortality is assumed to occur prior to other events in a model cycle.

42. Please explain why patients CKD0-2 in the model have a utility score of 1.0 (perfect health).

Alexion Response:
These are EQ-5D score transformed into health utility for five patients (three with complete data) in CKD stages 0-2 at day 164 in the trial. A value of "1.0" is an unusually high health utility score. However, we used the data as they were recorded in the trials. Such outcomes are not to be unexpected with small samples from ultra-rare diseases. From discussions with experts, it is not implausible that after alleviation of symptoms of aHUS, patients would feel relatively so much better compared to their pretreatment states that values of "1.0" could be recorded.

Importantly, note that in our base case, we use the health utility decrement described in Table 2 of Legendre et al. as the distance between SOC and eculizumab health states; this distance is determinative of the QALY gain, as well as changes in lifespan, in the eculizumab and SOC groups.

43. Please justify why 3.6% of the modelled population is still alive at age 100 years. Why does the model use 5-year banded mortality rates?

Alexion Response:
Per UK life tables, 1.1% of males and 2.8% of females in a birth cohort would be expected to be alive at age 100. Our slight absolute over-prediction is based on not modelling mortality changes after the age 85-95 interval, and using 10-year average transitional probabilities for background mortality. Examples of cost-utility models in the *Handbook of Health Economic Evaluation Series* (Oxford University Press) use banded intervals. The material effect on outcomes of using different, more precise, transitional probabilities for background mortality would be negligible due to discounting.

44. Table D4 includes a column which appears to describe standard deviations rather than standard errors. The same appears to be the case in the model. For all parameters in which standard deviations have been used, please provide either standard errors or sample sizes.

Alexion Response:
The only inputs for which we present standard deviations in Table D4 are cost data inputs; these standard deviations are assumed. We do not have access to statistics other than means on these data. We assume a broad degree of uncertainty around the parameter input by using the standard deviation and assuming a coefficient of variation of 1 in the probabilistic sensitivity analysis (PSA).

45. The model uses bootstrapping within the uncertainty analysis. Bootstrapping tells us about variability in the sample rather than uncertainty in the population parameters. Please explain why standard methods were not used e.g. sampling multinomial data from Dirichlet distributions with non-informative priors.

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Bootstrapping is widely used to estimate standard errors and confidence intervals[1], which relate the likelihood that the estimated mean is approximate to the true population mean. It is a well-known method, presented transparently in our analysis.

The Briggs, Ades and Price[2] 2003 present a means for estimating multinomial probabilities when some cells could be zero. This is a reasonable approach, and we think the authors authoritative, and the journal Medical Decision Making to be excellent and too often overlooked. In Briggs et al., they present a stylized example of N=2,000+ patients in two arms, distributed over 5 states. Their empirical problem is that none of the 2,000+ patients were observed in the HEX (hospital-managed exacerbation) state, but such an outcome was known to be possible for asthmatic patients. They use non-informative priors in a Bayesian framework, and the Dirichlet distribution, as a solution to their empirical problem.

However, there is more than one to approach this issue, and our method for doing so requires fewer assumptions. We bootstrap a sample of N=37 over 6 CKD states. Given that aHUS is an ultra-rare disease, far less is known about the set of potential outcomes than in asthma. Parameterizing "non-informative priors" would affect our model outcomes substantially more than in Briggs et al., simply because our sample size is much smaller, and the leverage of the non-informative priors would be much greater. Briggs et al. assume a uniform distribution for their Bayesian prior; our bootstrap does not require such an assumption be made. Finally, the distribution of CKD states in aHUS is based on a small amount of data; the influence of a choosing the wrong parametric distribution could be significant (i.e., what if the Dirichlet distribution assumed on the posterior is wrong? What if the uniform distribution on the prior is wrong?). Thus, we chose a non-parametric option.

If NICE would like, we will redo the PSA using the Briggs et al. approach. We would expect that the resultant PSA outcome would be nearly identical to that presented in our September dossier.

46. Please explain why several of the cost parameters (e.g. plasmapheresis, eculizumab administration costs) are held fixed at their point estimates?

Alexion Response:
We felt that these parameters should not be varied in the PSA, given that they are part of the price of the comparator and intervention, and there are no data to support what their second statistical moment would be. We did vary plasmapheresis in univariate sensitivity analysis. Administration costs would not be expected to exert much leverage on the outcome variable.

47. For the excess death rate for SOC please clarify why "solver solution for death at 1.5 years" (value = 0.177) was used, when the submission states that the model used a mortality rate of 0.13 from Coppo *et al* (2010) for death at 1.5 years.

[1] For example, see Guan W. From the help desk: Bootstrapped standard errors. The Stata Journal. Volume 3 Number 1: pp. 71-80. Abstract. Bootstrapping is a nonparametric approach for evaluating the distribution of a statistic based on random resampling. This article illustrates the bootstrap as an alternative method for estimating the standard errors when the theoretical calculation is complicated or not available in the current software.
[2] Briggs AH, Ades AE, Price MJ. Dirichlet distribution with Probabilistic Sensitivity Analysis for Decision Trees with Multiple Branches: Use of the Dirichlet. Med Decis Making 2003 23: 341

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Alexion Response:
Thank you for the comment; the team rightly points out a transcription error in the Excel spreadsheet. What reads: "Solver solution for death at 1.5 years to be 0.177" should read "Solver solution for death at 1.5 years to be 0.13". In other words, setting the excess non-renal mortality to 4% makes the overall SOC mortality to be 13% at 18 months, which is approximately equal to what was observed in Coppo et al. To be clear, no results are affected by this transcription error.

48. Please provide the timings of the 25 transplants in the 16 patients used to calculate the SOC transplant rate i.e. how many days from diagnosis did they take place? Please clarify how the SOC transplant rate was calculated.

Alexion Response:
The transplant calculation was simple: number of transplants observed in the entire pretreatment period divided by number of six-month increments in the entire pretreatment period. Data on the timing of the transplants were not considered—owing to the small sample size, a constant risk of transplant, which is the simplest assumption, seemed appropriate.

The diagram below demonstrates the timing of the transplants.

[redacted]

[redacted]

49. Please provide the supplementary data tables from Fremeaux-Bacchi et al (2013).

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The supplementary data tables are detailed in the attached file named "Fremeaux-Bacchi 2013 CJASN Suppl.pdf".

50. Page 17 of the submission states *"eculizumab for the treatment of aHUS represents good value for money"* yet the subsequent mention only clinical criteria and do not discuss cost. Please clarify the criteria used to make this judgement.

Alexion Response:
Alexion believes that eculizumab represents good value for money within the paradigm of value assessment in very rare diseases. As NICE has recognised in the alternative review process for highly specialised technology programme, incremental cost effectiveness analysis is not appropriate when applied to ultra-rare diseases. In the published literature, alternative assessment processes for ultra-rare diseases have proposed considering the value criteria below (Hughes Wilson 2012; Sussex 2013; European Commission 2013):

- Magnitude of clinical benefit (for example, disease modifying or life-saving nature of treatment);
- Response rate (percentage of treated patients who obtain benefit);
- Quality of the evidence in support of the benefit;
- Severity of the disease and availability of effective alternative treatments; and
- The impact on the disease on others beyond the patient.

Against these criteria eculizumab represents a very high degree of added value. Eculizumab is a transformative and life-saving therapy for patients with aHUS, enabling a substantial improvement in health through the correction of the underlying disease. [redacted]. Further, 100% of patients treated with eculizumab achieve inhibition of uncontrolled complement activation, the underlying pathologic defect causing morbidity and premature mortality in aHUS patients. The quality of clinical data and proof of clinical effect is strong for a condition of such rarity, with four trials with follow-up times in excess of two years. By improving patient outcomes, eculizumab allows patients and their families to regain their lives in a way that restores function, productivity, and quality of life.

The added-value of eculizumab is especially important when considered against the unmet medical need in the aHUS patient population who are often young. As noted in our submission, 65% of all patients die, require dialysis, or have permanent renal damage within the first year of diagnosis while on PE/PI or dialysis and a progressive increased mortality rate thereafter.

This high added-value must be considered in light of the overall budget impact and affordability of the investment required to obtain this benefit. Given the very small patient population in the UK, and considering the cost offsets associated with lower use of expensive SOC interventions, the net investment required for eculizumab is affordable and justified by the magnitude of benefit.

Section C: Textual clarifications, additional points and additional data requests

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51. **Priority question:** Please state expected dates for the final analyses of ongoing studies mentioned in Table A4.

Alexion Response:
The following are the expected dates for the finalization of on-going studies mentioned in Table A4:

Study	Database Lock	CSR Finalization
C10-003	[redacted]	[redacted]
C10-004	[redacted]	[redacted]
C11-003 (Long-Term Follow-Up)	[redacted]	[redacted]
M11-001 (Registry)	Open	Open

52. **Priority question:** The submission mentions Clinical Study Reports (CSRs) for the eculizumab studies. In particular, Section 9.7 states that *"Complete AE listings are available in the respective clinical study report"* and *"Additional details regarding AEs are available in the clinical study report."* These reports have not been submitted to the ERG but appear to contain AE data not reported in the submission. Please provide the CSRs.

Alexion Response:
Per the following text in the "Instructions for Manufacturers and Sponsors" section of Appendix G that states: "Clinical trial reports and protocols should not form part of the submission, but must be made available on request," we did not include the Clinical Study Reports (CSRs) with our initial submission. However, we have provided them upon the ERG's request.

Please find attached the following CSRs:

- 2012 Eculizumab Safety and Efficacy Update Report for aHUS Patients 28Sep2012;
- C08-002AB CSR 04Mar2011;
- C08-003AB CSR 04Mar2011;
- C09-001r CSR 08Mar2011;
- C10-003 Interim CSR 27Aug2013; and
- C10-004 Interim CSR 28Aug2013.

53. **Priority question:** For each patient in studies C08-002 and C08-003, please provide patient-level EQ-5D utilities at baseline and at each possible timepoint.

Alexion Response:
The figures in the following graphic depict the mean change in EQ-5D scores and the number of available results at each point for the prospective studies. In both prospective studies, quality of life (QoL) was significantly improved early on in treatment duration, and the improvements were clinically important and sustained during long-term eculizumab treatment. In both prospective studies, the EQ-5D data indicate a gain in patient health.

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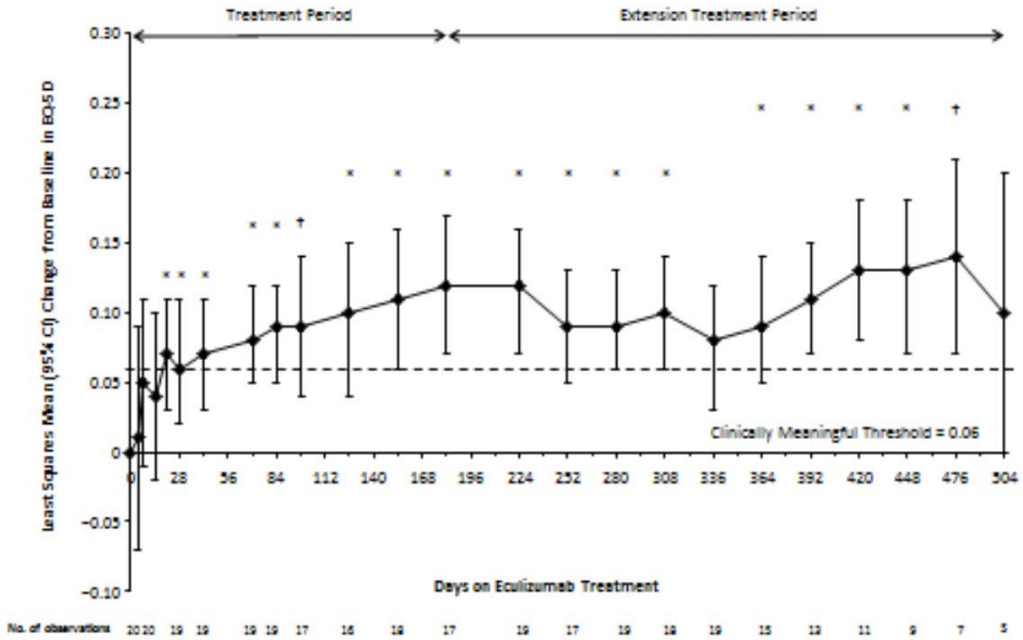
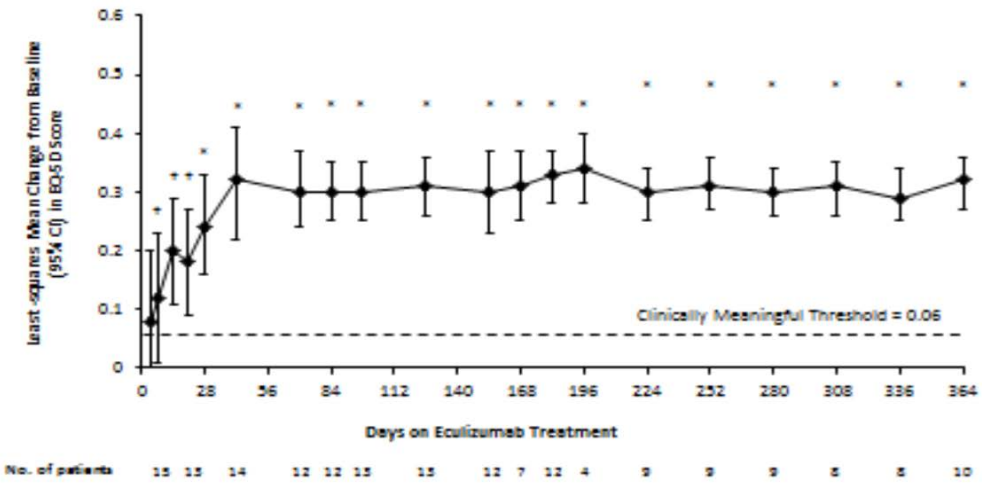
Study C08-003: Change in EQ-5D score



In study C08-003, the median duration of eculizumab treatment at the most recent data-cut off (shown in the figure above) was 62 weeks. From 336 days of treatment, the number of available data points decrease as not all patients had been treated for longer than this time period at data cut-off. Nineteen patients remained on chronic eculizumab treatment in the extension phase of the study (after the initial 26 week treatment period).

Study C08-002: Change in EQ-5D score



In study C08-002, the median duration of eculizumab treatment at the latest data-cut off (shown in the figure above) was 64 weeks. Fifteen patients completed 26 weeks of

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treatment (two patients were withdrawn—one patient due to an adverse event unrelated to eculizumab and one met an exclusion criterion). Of these 15 patients, 13 continued on long-term treatment in the extension phase.

54. Please clarify why it has not been possible to undertake a randomised controlled trial of eculizumab versus standard care.

Alexion Response:
Formal comparisons between aHUS patients treated with eculizumab and similarly-matched patients treated with supportive care would be very difficult due to the nature of aHUS as an ultra-rare and life-threatening disease. A comparison between placebo and treated patients is considered inappropriate by ethics committees and regulatory agencies that have established formal processes to evaluate drugs used to treat severe, ultra-orphan diseases. Given the established accelerated mortality and progression of the disease from diagnosis despite PE/PI (65% patients die or progress to ESRF or renal damage within 1 year of clinical evidence of TMA), asking physicians and patients to provide unproven supportive care during this period of time, when an approved and proven treatment is available, it is not reasonable and in fact impossible to expect physicians to put their aHUS patients at risk for death or ESRF at this point of the available medical evidence for eculizumab.

The design of the two eculizumab prospective studies for aHUS was agreed to in full consultation with the FDA and EMA based on the impracticality of designing and recruiting a sufficient number of aHUS patients for placebo-controlled studies, as well as several published case studies that illustrated the positive response of aHUS patients to eculizumab treatment at the time of consultation.(Nurnberger et al, 2009)

55. The submission makes several references to the proposed Homecare service (pages 17, 46, 57 and elsewhere in the submission). Please provide more details on this scheme.

Alexion Response:
The homecare scheme referred to in the submission document is currently available for patients receiving eculizumab therapy for aHUS. This service would be made available to all patients receiving eculizumab for the treatment of aHUS in the same way that patients receiving eculizumab for paroxysmal nocturnal haemoglobinuria (PNH), a nationally commissioned service, have done since the UK launch of eculizumab for PNH in 2007.

The abstract below provides more information about the homecare service delivered to PNH patients in England; this is the model that will be adopted for aHUS patients. The mechanism of service contracting is yet to be determined for aHUS pending discussions and the eventual outcome of NHS England's aHUS service designation and tender for services within England. Until such time as the aHUS service has been defined (as in the case of PNH as noted below), all services for homecare will be directly contracted with each NHS Trust where aHUS patient(s) would benefit from such service.

As described in our submission, it is anticipated that the majority of aHUS patients will transition to homecare in England, which is entirely funded by Alexion Pharma UK Ltd and as such, services are zero rated for VAT, providing a savings of 20% to the NHS in terms of drug procurement costs. Additional cost savings would be realised to the NHS as all ordering, delivery, and infusion administration costs are contained within the

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homecare service costs. Savings would also be realised by patients, carers, and families given that homecare services are delivered at an appropriate place for the patient (for example, home or workplace), thus removing travel and travel-related costs.

Abstract: Continued Benefit From Prolonged Treatment with Eculizumab in 130 Patients with PNH in the UK: Home Delivery of Eculizumab Is Safe, Convenient and Associated with Very High Levels of Patient Satisfaction

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“Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired bone marrow disorder characterised by intravascular hemolysis with resultant anemia often leading to transfusion dependence, severe disabling symptoms and, frequently, life threatening thrombosis. Historically the management of PNH was largely supportive, relatively ineffective and resulted in frequent visits to hospital, admissions, an inability to function normally including loss of employment or other daily activities. PNH is a chronic condition and in most patients persists for the remainder of the patient’s life. Eculizumab was first used for PNH in 2002 and has been licensed since 2007. Eculizumab has been reported to improve all symptoms due to hemolysis in PNH as well as preventing the common complications, such as thrombosis and renal failure and normalising survival. However eculizumab has to be given as an intravenous infusion every 2 weeks indefinitely.

In the UK PNH is managed in a shared care model between local hematologists and the National PNH Service from two Centres based in St James’s University Hospital, Leeds and Kings College Hospital, London. Here we report the management of patients treated with eculizumab within the PNH National Service. A total of 130 patients have been treated with eculizumab since May 2002 with 120 currently receiving therapy. 5 patients have died and none were directly related to PNH or eculizumab. 99 patients requiring transfusions prior to eculizumab have been on treatment for at least a year and 65 (66%) of these have not required transfusions for at least the last 12 months. The rarity of PNH means that patients frequently have to travel long distances for review and treatment. This leads to major issues both in terms of time commitment and expense. In order to allow patients to lead as normal lives as possible we have developed a service model in which Specialist PNH Clinics are performed regionally by the PNH Centre and in which patients receive eculizumab every 2 weeks in their homes delivered by a homecare nursing team. In the UK, the PNH Service and Healthcare at Home Ltd (www.hah.co.uk) have been working in partnership for over 7 years during the clinical trials of eculizumab and since its license in 2007. The PNH Service manages the prescription and delivery of eculizumab including an education program for the homecare nurses. This innovative home infusion programme ensures the safe administration of eculizumab outside of the hospital environment, leading to enhanced treatment-associated convenience for patients and their families. Each year the home infusion program has grown, now over 3000 infusions are given annually including whilst patients are on holiday, visiting family, at University or in the workplace.

A recent patient survey has been conducted from the two PNH Centres to assess the patients’ experience of their PNH diagnosis and treatment. 122 patients responded with 70 of these patients receiving treatment with eculizumab and all currently on the home infusion programme. 63 of 68 patients reported the homecare service as excellent or very

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good compared to 1 reporting it as poor and 66 of the 68 patients preferred to have their treatment at home compared to hospital. The patients' main concerns before starting treatment were reduced life expectancy and the requirement for blood transfusions along with fatigue. With eculizumab treatment and the convenience of homecare 30 patients reported being able to return to work. The homecare service is supported by contact between the clinic appointments, 56 of 67 patients having contact with their PNH Specialist Centre by phone or email in addition to the care of the patient's local hematology team that over 90% of the patients continue to see. The impact of PNH on patients' lives before eculizumab treatment was rated and improved from a median of 3 out of 10 (0 = no quality of life; 10 = normal) prior to eculizumab to a median of 8 out of 10 on treatment. In summary, a novel model of provision of care in PNH with Outreach Specialist Clinics, a 24 hour on call service and homecare delivery of eculizumab permits the normalisation of patients' lives and overcomes most of the hurdles associated with prolonged regular intravenous therapy. This allows patients to benefit fully from eculizumab including reduction in transfusions, the prevention of serious complications, normalisation of quality of life and where appropriate a return to work."

References Used in Above Response (beyond those included in September 2013 submission)

Note: PDF copies of these articles have been provided to NICE.

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Turnberg, D., Botto, M., Warren, J., Morgan, B., Walport, M., & Cook, H. 2003. CD59a Deficiency Exacerbates Accelerated Nephrotoxic Nephritis in Mice. *Journal of the American Society of Nephrology*. 14, 2271-2279.

Vilalta, R., Lara, E., Madrid, A., Chocron, S., Munoz, M., Casquero, A., & Nieto, J. 2012. Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome. *Pediatric Nephrology*. 27:2323–2326.

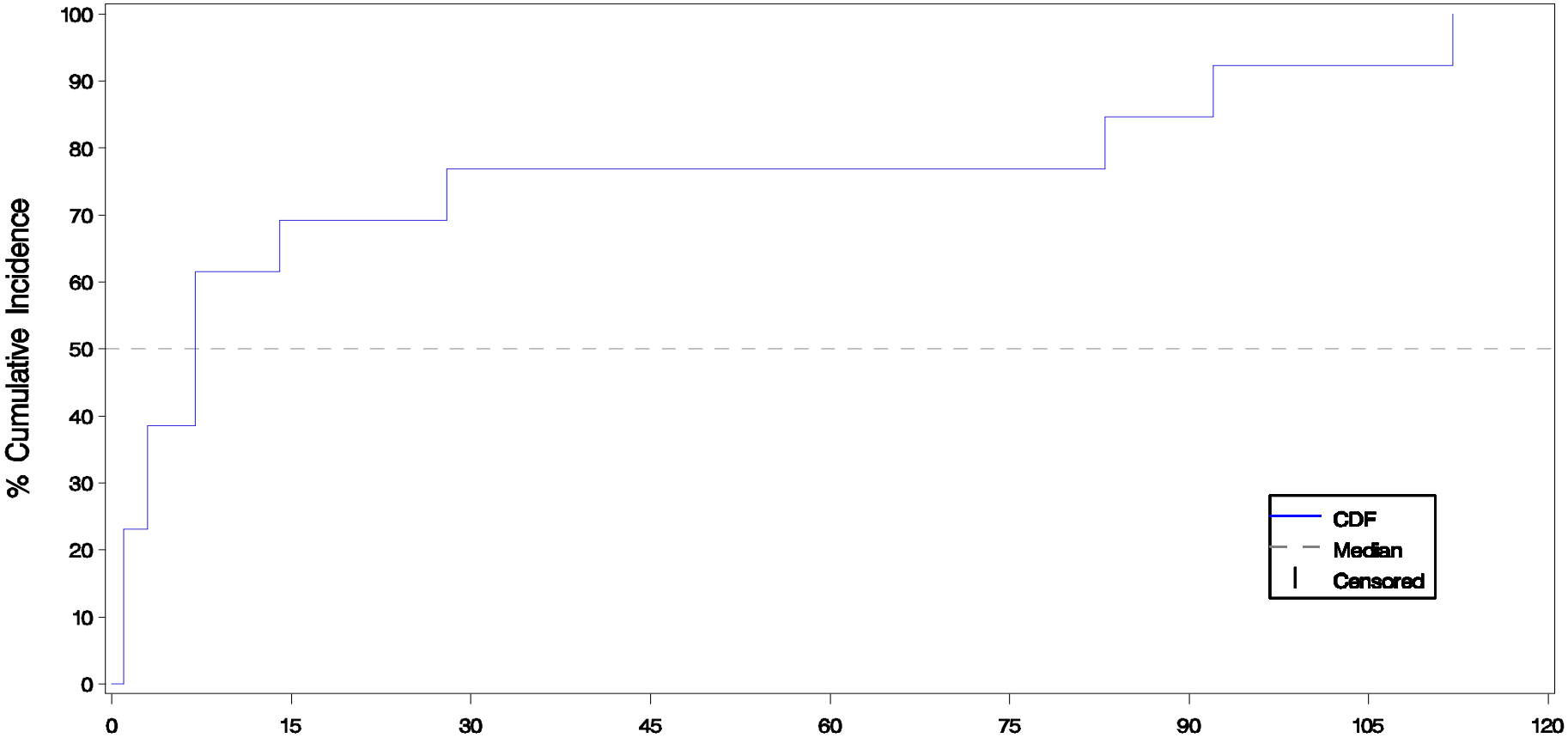
The following reference was accidentally omitted from the complete reference list in our September 2013 submission. We provide the full reference below, and a PDF copy with the above references.

Wood, C. & Grant, E. Counting the Cost, London: Demos 2010. Available at www.demos.co.uk. Accessed October 11, 2013.

Appendix 1 - Kaplan-Meier curves

Protocol C08-002:

Figure 5.1
Platelet Count Normalization – Time to First Occurrence (Only responders with abnormal values at baseline shown)
Intent to Treat Population N=13



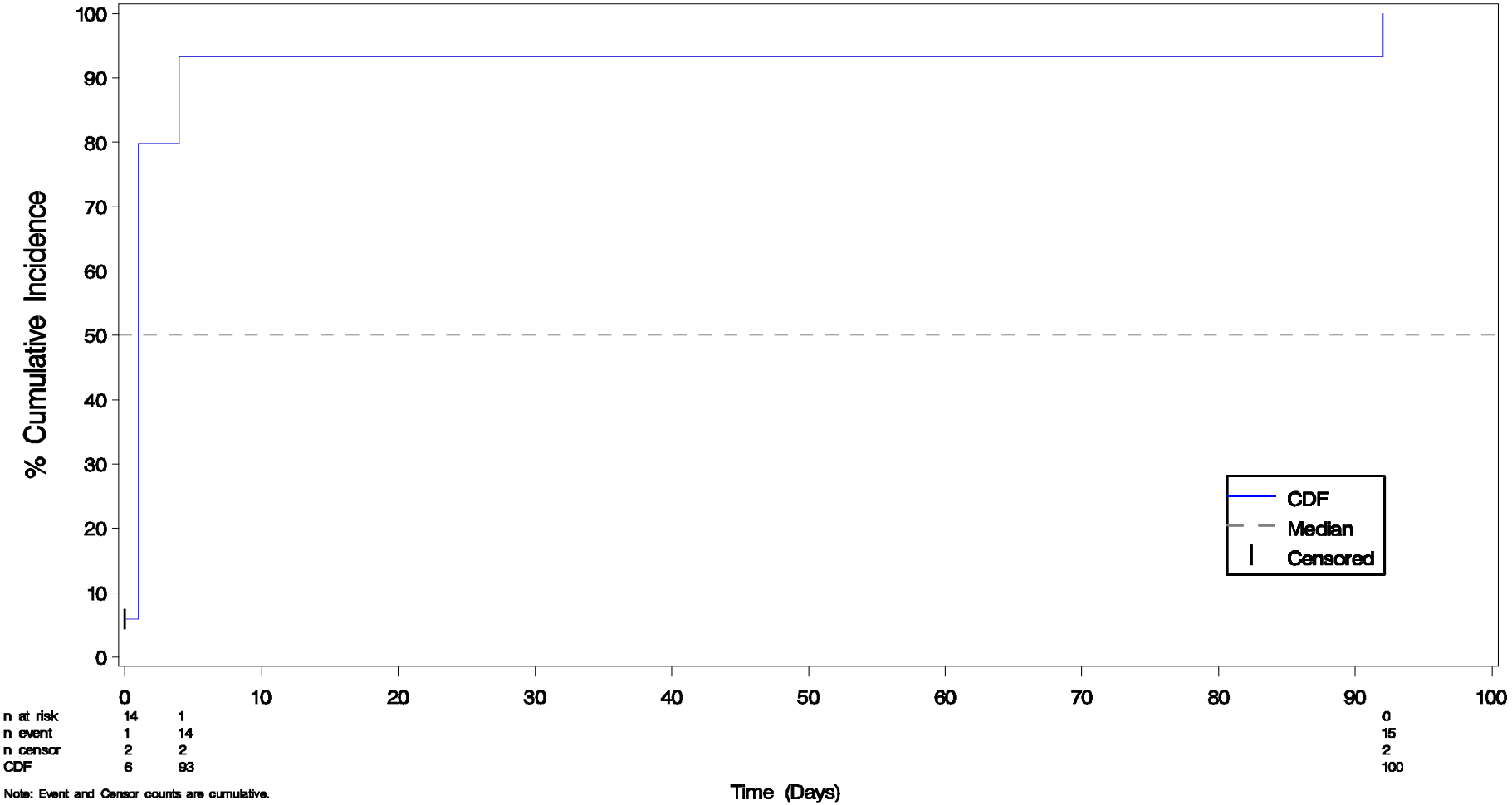
n at risk	13	8	5	4	3				2	1		0
n event	0	5	8	9	10				11	12		13
n censor	0	0	0	0	0				0	0		0
CDF	0	39	62	69	77				85	92		100

Note: Event and Censor counts are cumulative.

Time (Days)

Protocol C08-002:

Figure 11.1
TMA Event−Free Status − Time to First Occurrence
Intent to Treat Population N=17

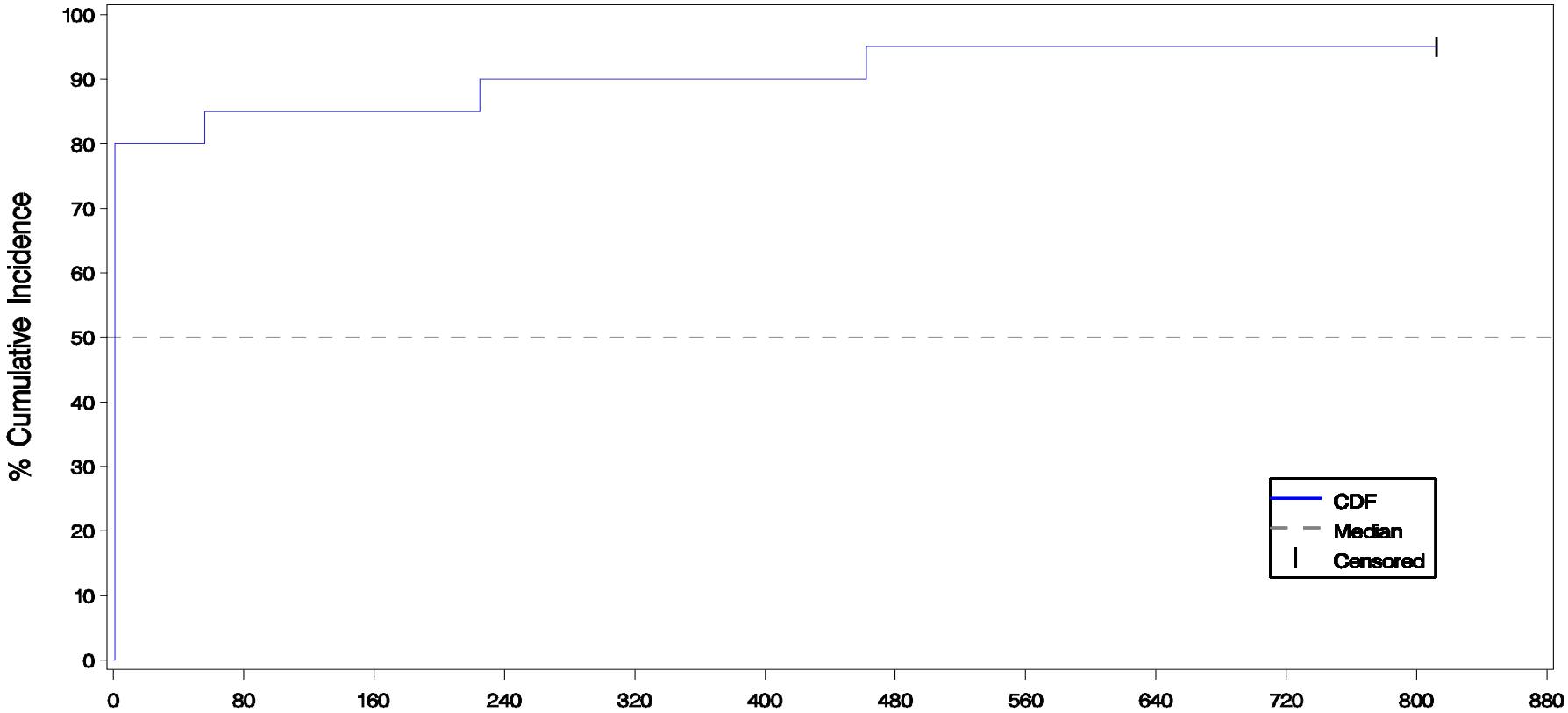


n at risk	14	1									0
n event	1	14									15
n censor	2	2									2
CDF	6	93									100

Note: Event and Censor counts are cumulative.

Protocol C08-003:

Figure 11.1
TMA Event−Free Status − Time to First Occurrence
Intent to Treat Population N=20

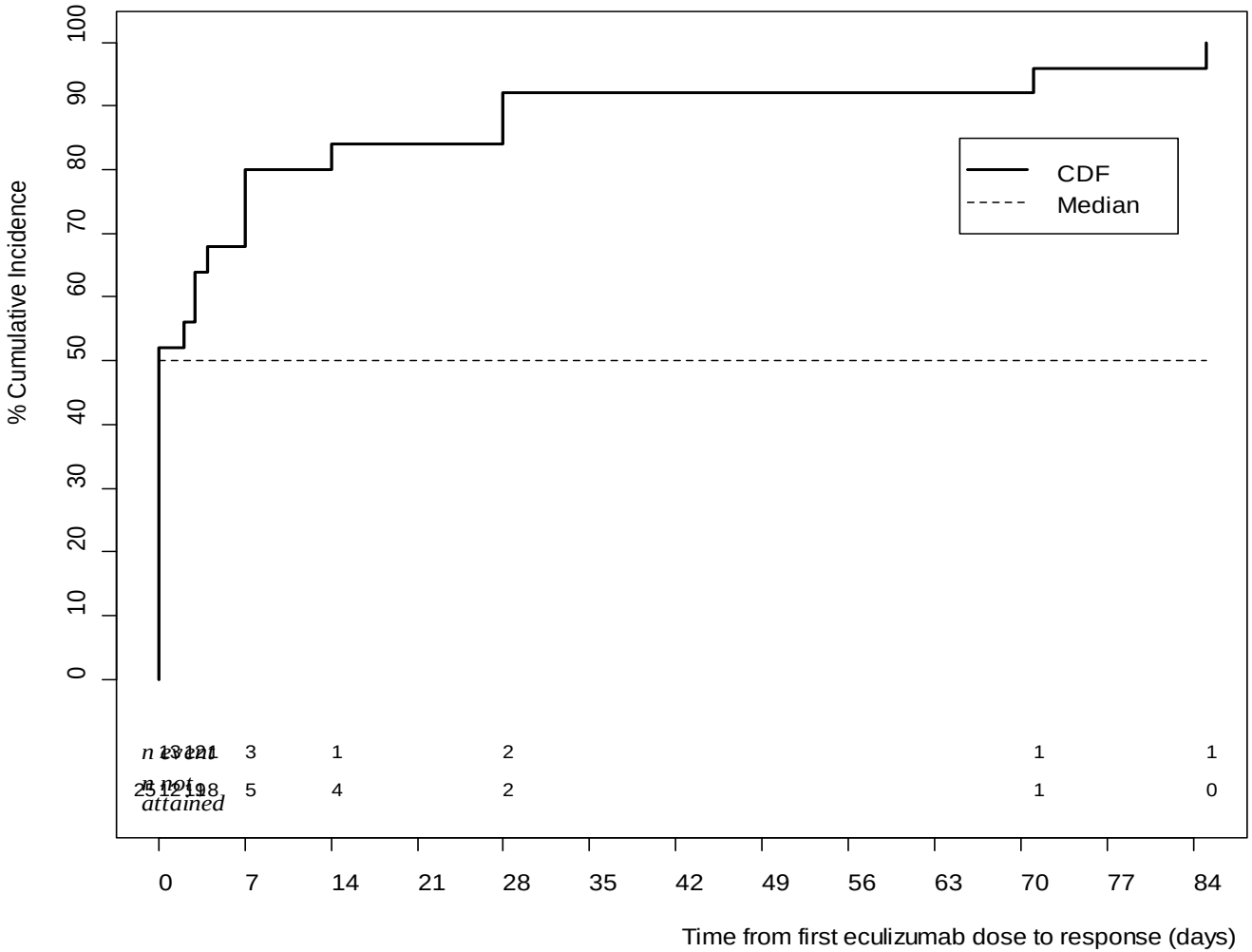


	0	80	160	240	320	400	480	560	640	720	800	880
n at risk	20	3		2			1				0	
n event	0	17		18			19				19	
n censor	0	0		0			0				1	
CDF	0	85		90			95				95	

Note: Event and Censor counts are cumulative.

Protocol C09-001r:

Figure 14.3.1 Platelet Count Normalization – Time to First Occurrence (Only Responders, N=25)



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