National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **26 November 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Alexion appreciates the opportunity to respond to the Economic Review Group's (ERG's) report and model prepared by The University of Sheffield School of Health and Related Research (ScHARR). In the extremely short time period (seven business days) Alexion was given to review the materials, a number of factual inaccuracies related both to the ERG's critique of the manufacturer's data and model, as well as several key errors in the ERG's own model have been identified. Whereas the ERG had two months to review the manufacturer's model and report, and to ask clarifying questions, Alexion has not had the same opportunity. As such, combined with the short review timeline, Alexion cannot be sure that other technical errors do not exist in the ERG's model. Alexion also did not have sufficient time to address each of the individual errors noted in the report; however, in an attempt to streamline comments for NICE and the Appraisal Committee, Alexion has grouped its responses to the most important factual inaccuracies into the following categories:

1. **Factual inaccuracies <u>in the structure and parameterisation</u> of the ERG's model (Issues 1, 4-6);**
2. **Factual inaccuracies <u>in terms of technical errors</u> in the ERG's model (Issues 2-3);**
3. **Factual inaccuracies <u>in the description of the manufacturer's model or documentation (Issues 7-19);</u>**
4. **Factual inaccuracies related to <u>systematic review, clinical data, and interpretation of decision problem (Issues 20-22)</u>; and**
5. **Factual inaccuracies related to the <u>impact of the technology beyond direct health benefits (Issues 23-24)</u>.**

Our responses illustrate that the results of the ERG's model, when corrected for several notable errors and factual inaccuracies, approximates the manufacturer model's outputs. As such, Alexion believes that most of the ERG's critique of the manufacturer's model is more stylistic than substantive, with most of the ERG's suggested changes, including those we consider to be valid, having only a minimal impact on results.

Issue 1 <u>Factual inaccuracies in the structure and parameterization of the ERG's model</u>: End-stage renal failure (ESRF) is not associated with excess mortality in the ERG's model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The structure and parameterization of the ERG's model suffer from a major problem that Alexion believes invalidates its outcome estimates. Specifically, the ERG contends that ESRF is a "pooling state" where a majority of modelled SOC	The ERG should update their model to include the UK Renal registry parameter for excess mortality,	ESRF is a highly morbid condition associated with tremendous mortality. This should be recognized in the ERG's model, as well as the infeasibility of assuming only a slight increase in mortality in ESRF patients. There are numerous high quality data publicly available,	This is not a factual inaccuracy nor is it a structural error in the model. The ERG report already highlights that the exploratory

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
patients exist for 40 model cycles or 20 years. This is contrary to commonly available clinical data, UK Renal Registry data, and the manufacturer's aHUS physician interviews. Instead, the ERG base the standard of care (SOC) arm in its model on the aHUS cohort described in Noris et al. 2010, claiming that these data are more representative than the pretreatment period of the eculizumab clinical trials sample (see also Issue 5 below). The ERG uses a model-fitting exercise so that the constant hazard to death, ESRF, and transplant can be fitted to the Noris et al data. The structural error in the ERG's model is that the likelihood of dying when patients are in dialysis/ESRF is incorrect, because its model is essentially over-fitted to the Noris et al. data. The ERG misinterprets the Noris et al. data (and disregards the manufacturer's discussion of these data in the Validation Section of the manufacturer's initial submission, Appendix G, pages 175-177) by assuming that patients were followed after entering ESRF. Noris et al. reports Kaplan Meier estimates to the *first event of ESRF or death* in Figure 2, which the	similar to the manufacturer's model calculation, for patients in ESRF.	including age-adjusted mortality rates from the UK Renal Registry used in the manufacturer's submission, supporting that any patient in ESRF is more likely to die than is reflected in the ERG's model. In fact, the rate could be even higher, considering that patients on SOC still have an underlying complement disorder. To obtain further validation of the excess mortality rate associated with ESRF, Alexion consulted a leading aHUS physician, Professor Tim Goodship, for expert advice. Specifically, the manufacturer asked Dr. Goodship the following questions and received the following replies: Question 1: Do you believe that patients with aHUS who are in ESRF have a death rate that is higher than an age and gender-matched normal population (i.e., no chronic disease identified and not on dialysis)? Answer 1: "Yes. For the UK there are numerous reports on this at the Renal Registry Website. For example see presentation at http://www.renalreg.com/Downloads/presentations.html and the report at http://www.renalreg.com/Report-Area/Report%202012/Chapter_5.pdf. I think that the UK Renal Registry data is excellent and you should use it." Question 2: If so, do you think that patients with aHUS who are in ESRF have a death rate equal to or greater than the average death rate for the average person in ESRF (e.g., the UK Renal Registry age-adjusted rate)? Answer 2: "Don't know but I suspect that the mortality is	model is over-fitted. Whilst the ERG sought more detailed information on the distribution of patients from Professor Noris, these data were unfortunately not available at the time of the assessment. The manufacturer is incorrect in stating that we used Kaplan-Meier estimates in Figure 2 of Noris *et al*. We used data from Table 2 in Noris which does not censor patients at the first event. The data in the table *do* take account of mortality after developing ESRF. The ERG believes that there is a problem in the manufacturer's use of 1-year survival from the UK Renal Registry to characterise the conditional probability of death given ESRF indefinitely within their model. One-year survival estimates may not apply over the longer term and appears to be highly dependent on age group (see

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG uses to estimate its lifetime model. This method does not take into account the mortality of patients after reaching ESRF; the ERG's model assumes that the likelihood of dying is the same for patients in CKD 0-2, CKD 3-4, and ESRF, which does not match outcomes observed in clinical practice. By making this incorrect assumption, the ERG's model calculates an extremely low six-month likelihood of dying from ESRF/dialysis (0.0051%). The problem with the ERG's assumption is best visualized in Figure 13 in the ERG's report which shows Markov traces for SOC patients and illustrates that patients pool in the ESRF state. For 59 model cycles or about 29.5 years, ESRF is the most likely outcome for an SOC patient in the ERG's model, meaning that a plurality of modelled patients is in ESRF. As noted above, the reason that pooling in ESRF occurs is because the ERG modellers only fit health state transitions to the Noris et al. data and do not consider other data. In short, the ERG modellers do not consider that ESRF, in and of itself, is a severe outcome associated with substantial mortality, which contradicts what is seen in clinical practice.		not different." When the ERG's model is modified using the UK Renal Registry data to indicate that aHUS patients in ESRF face an age-adjusted excess mortality rate, the results of the ERG's model approximate those calculated by the Alexion model and the majority of the difference in outcomes of the manufacturer's model and the ERG model disappear. Specifically, the SOC Life Years Gained (LYGs) and Quality-Adjusted Life Year (QALYs) predicted by the ERG's model both decrease by 42%.	remainder of the registry report chapter 5, particularly page 106 Figure 5.5, page 107 Figure 5.6 and page 108 Figure 5.12). The UK registry report itself states that the median life years remaining for incident patients aged 25-28 years is 18 years. Applying the probability of 5.2% (which excludes other cause mortality) to an incident cohort would appear to substantially overestimate mortality in the population (estimated survival = ~9.37 years). Adding in other cause mortality would skew the results further. The ERG would therefore advise against applying this rate indefinitely. It is also worth noting that the UK renal registry reports survival for an incident cohort of patients with ESRD aged 18-34. At 10 years, the probability of survival is approximately 0.82. Within the fitted standard care arm of the ERG model, assuming

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There are numerous, high quality peer-reviewed published data that disprove the ERG's assumption and illustrate the excess mortality associated with ESRD/ESRF/dialysis. Conversely, Alexion is unable to find data illustrating no excess mortality for patients with ESRF. In the manufacturer's model, the six-month probability of dying when in the ESRF state was derived from the UK Renal Registry 15th Annual Report (2012): Chapter 5 Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011: national and centre-specific analyses which states: "One year age adjusted survival for prevalent dialysis patients improved to 89.8% in the 2010 cohort from 89.1% in the 2009 cohort." The 95% confidence interval for these data is: 89.3–90.2, based on a sample size of N=25,685. The 5.2% six-month mortality probability calculated in the manufacturer's model is derived directly from these data. The ERG does not comment on the validity of the six-month probability of dying for ESRF patients used in the manufacturer's model. Importantly, however, the ERG uses this parameter			that all patients enter the model in ESRD, survival at 10-years is approximately 0.80. Given this information, the fitted model appears quite reasonable in predicting survival in this cohort of patients. In summary, we implemented the model as intended, this is not a structural error and the model predictions are supported by the UK renal registry data.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
in its own model, but *only for patients undergoing transplant*. Using the probability for the transition for transplant patients, but not for patients in ESRF, is not explained anywhere in the ERG's report. More importantly, the ERG upholds its Noris et al-based data fitting approach, which leads to counterintuitive results contrary to consistent research findings on ESRF mortality. The UK Renal Registry does not break out survival for patients in ESRF who have a rare, highly morbid and deadly blood disorder like aHUS. However, Alexion discusses aHUS and dialysis on page 144 of the manufacturer's submission (Appendix G), including a paragraph on how the causes of death while on dialysis overlap with the systemic complications due to complement-mediated TMA in aHUS patients. Again, given the mechanics of dialysis and pathology of kidney failure, Alexion is aware of no set of patients who could withstand decades of ESRF without excess mortality. The effects of this omission from the ERG's model are critical—when implementing a "fix" to the ERG's model using the UK Renal			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Registry mortality rate, the results produced by the ERG's model begin to approximate the results of the manufacturer's model as the SOC LYGs and QALYs calculated in the ERG's model both decrease by 42%.			

Issue 2 <u>Factual inaccuracies in terms of technical errors in the ERG's model</u>: The ERG counted only one-half of the costs of SOC, but all costs for eculizumab.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG only counts half of SOC costs in its model, but counts all costs for eculizumab. The error occurred because of the ERG's correct use of the half-cycle for eculizumab patients, but an incorrect use of it for SOC-treated patients, which biases the ERG's model against eculizumab. For example, cell BA6 on the sheet 'StandardCareMarkov' in the ERG model uses the following formula: "=**0.25***M6*Parameters!$C$31". This formula is supposed to represent the costs of the SOC patients in ESRF in the second model cycle which lasts 6 months. Cell BA6 on the sheet 'EculizumabMarkov' in the ERG model uses the following formula: "=**0.5***M6*Parameters!$C$31". This formula is supposed to represent the costs	The ERG should correct this error in its model and report by changing the 0.25 to 0.5 in the columns "AZ-BD" on the 'StandardCareMarkov' sheet.	No justification exists for counting one-half of SOC costs while counting all eculizumab costs in the ERG's model. Not only is the calculation incorrect for SOC patients, but the effect biases the model inappropriately against eculizumab.	The manufacturer is correct and the ERG thanks them for raising these issues – these were unintentional errors and no bias was intended, either for or against eculizumab. We have amended the model accordingly in the final report. The incremental costs are not materially affected. The ERG does however note that the problems with the manufacturer's model necessitated the development of a new model. This is not ideal as the timescales for the HST appraisal process do not accommodate such additional work.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
of the ECU patients in ESRF in the second model cycle. The inputs M6 (% in ESRF in the second model cycle) and Parameters!$C$31 (the cost for one year of ESRF treatment) are correctly linked/calculated. But, then the SOC calculation includes a quarter year of costs (**0.25**) while the eculizumab calculation includes a half year of costs (**0.5**). This error continues throughout the cells in columns “AZ-BD” on the 'StandardCareMarkov' sheet after the first cycle, effectively reducing SOC costs by half while keeping eculizumab costs at 100%. It appears as though the model developer did not correct the half cycle adjustment in the SOC arm of the model, but did so only for the eculizumab arm.			

Issue 3 **<u>Factual inaccuracies in terms of technical errors in the ERG's model</u>: The ERG excludes *entirely* the cost of plasmapheresis (PE/PI) from the cost of SOC.**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In addition to only counting half of SOC costs as described in Issue 2 above, the ERG excludes entirely the cost of plasmapheresis (PE/PI) from the cost of SOC. Specifically, Column "BD" in the 'StandardCareMarkov' sheet is not part of the sum in column "BF", which should account for total costs of all components of SOC. Although the costs for eculizumab are counted in full in the ERG's model, costs of plasmapheresis (PE/PI) —one of the most expensive components of SOC—are totally excluded, which inappropriately biases the model against eculizumab.	The ERG should correct this error in its model and report by making Column "BD" in the 'StandardCareMarkov' sheet part of the total sum in column "BF".	No justification exists for the ERG to exclude plasmapheresis (PE/PI) costs, which is an expensive component of SOC, from its model.	See response to issue 2. This error has been corrected in the model.

Issue 4 **<u>Factual inaccuracies in the structure and parameterization of the ERG's model</u>: The ERG's use of a discount rate of 3.5% for costs and benefits is not aligned with the NICE Methods Guide.**

Description of problem	Description of proposed amendment	Justification for amendment	
The discount rate of 3.5% for costs and benefits used by ERG is inappropriate according to the NICE guidelines. As quoted in the manufacturer's submission (Appendix G), the NICE guide to the	The ERG should update its model to include a discount rate of 1.5% for	Based on the model the ERG submitted, the incremental QALY gains for eculizumab are very large (26 QALYS when undiscounted; 10 QALYs when	This is not a factual inaccuracy. The preferred discount rate within HSTs is not yet clear. In the

Description of problem	Description of proposed amendment	Justification for amendment	
methods of technology appraisal 2013 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."(Section 6.2.19 of the NICE Methods Guide to the methods of technology appraisal. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed September 8, 2013.) A precedent was set for using the 1.5% discount rate for health benefit during the NICE evaluation of mifamurtide for osteosarcoma. In this review, NICE accepted a discount rate of 1.5% for QALYs and 3.5% for costs on the grounds that criteria similar to those included in the NICE Methods Guide were applicable. For eculizumab, the ERG model assumes a discount rate of 3.5% for both costs and benefits, implying that the ERG does not accept that	benefits instead of the 3.5% used.	discounted at 3.5%). Plus, when correcting for the above identified errors in the ERG's model, there is even greater evidence that "long-term health benefits are likely to be achieved," based on higher incremental QALYs (e.g., from assuming an excess mortality likelihood from ESRF). This further justifies the use of a 1.5% discount rate as outlined in the NICE guidelines where it is stated "a 1.5% discount rate should be used if "long-term health benefits are likely to be achieved".	absence of clearer guidance, the ERG believe that the choice of appropriate discount rate lies with the Appraisal Committee therefore it would have been helpful for the manufacturer to present results for discount rates of 1.5% and 3.5%. This was not done in the MS. The choice of discount rate will either make incremental costs appear lower and incremental QALYs higher, or make incremental costs higher and incremental QALYs lower. It is unclear how such information will be used. Given this uncertainty, both sets of analyses are presented by the ERG so that the Committee can decide the basis of their decision-making.

Description of problem	Description of proposed amendment	Justification for amendment	
eculizumab meets the criteria in the NICE Methods Guide. This is surprising given that the ERG's base case model (without correction of errors described herein) estimates an undiscounted incremental life gain of 18 years (54 years gained on eculizumab vs. 36 years gained for SOC) and 26 QALYs gained. When discounted at 3.5%, these gains fall by more than half, representing the situation described above in the NICE Methods Guide where "cost-effectiveness analyses are very sensitive to the discount rate used". Furthermore, the gain in undiscounted and discounted life years and QALYs is substantially higher for the use of eculizumab in aHUS than for mifamurtide in osteosarcoma as reported in the ERG report for TA235, where the incremental QALY gain was less than 3 QALYs under all scenarios. Indeed, the incremental QALY gains with eculizumab in the ERG model are large relative to any published cost effectiveness analysis. For example, see "Table D23: Comparative QALY gains from select cost-effectiveness analyses publications" in the manufacturer's submission (Appendix G), which lists QALY gains reported in Tufts University's Cost-effectiveness Registry, which provides systematic review of cost-effectiveness results from studies published since 2003 in any journal whose impact factor is ≥10. Across 14 studies, changes in QALYs ranged from -0.05 (heparin sodium and alteplase for haemodynamically stable			

Description of problem	Description of proposed amendment	Justification for amendment	
patients with a sub-massive pulmonary embolism and right ventricular dysfunction) to 3.0 (implantable cardioverter defibrillator to prevent sudden cardiac death for patient who are at risk for sudden death due to left ventricular systolic dysfunction). An argument could be made for the use of discount rates of 1.5% for health gains and 3.5% for costs when appraising eculizumab, as these were the rates used by NICE when appraising mifamurtide. Alexion chose to be conservative in its submission by using the 1.5% discount rate for both costs and benefits as stated in the NICE Methods Guide. It may be helpful to demonstrate to the Appraisal Committee the effect on costs and QALYs gained by using the same discount rates as were accepted for mifamurtide in osteosarcoma.			

Issue 5 <u>Factual inaccuracies in the structure and parameterization of the ERG's model</u>: The ERG disregards Coppo et al. and Hovinga et al., which are large, well-designed cohort studies with minimal justification.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Coppo et al. and Hovinga et al. are large, well-designed and conducted cohort studies. The ERG excludes data from these studies in its analysis with minimal discussion. On page 48 of the ERG report, it's stated: "The presented results for Fremeaux-Bacchi et al and Noris et al are for aHUS patients. Results for Hovinga et al and Coppo et al are presented for the ADAMTS13 ≥10% and detectable ADAMTS13 subgroups respectively. There are likely to be differences in prognosis and outcomes between aHUS-specific patients and other populations." This comment fails to acknowledge that the criteria used for the submitted analysis to identify aHUS patients within the Coppo and Hovinga cohorts are closely aligned to the inclusion criteria for the eculizumab clinical trials and the diagnostic algorithm presented in the manufacturer's submission. Aside from speculating that non-aHUS patients could be in these subgroups, the ERG does not address these studies, despite the diagnostic criteria used to identify these subgroups being more similar to the indicated use of eculizumab for aHUS than the selection criteria in Noris et al. and	The ERG should use Coppo et al. and Hovinga et al. as the base case parameter for excess non-renal death in the ERG's model. At the very least, the Coppo and Hovinga data should be included as a sensitivity analysis in the ERG's model.	Alexion used the TMA registry data from Coppo et al and Hovinga et al to validate both the CKD-based model and non-renal mortality its model. While use of registries can have inherent limitations to estimate incidence and prevalence of clinical complications, Alexion believes both of these TMA databases identify and follow aHUS patients as defined and enrolled in the FDA and EMA-approved eculizumab registration trials. More importantly, for modelling purposes, these registries consecutively and non-selectively recruit aHUS patients in order to better evaluate aHUS patient outcomes with supportive care and treatment with eculizumab and therefore avoid selection biases seen in other aHUS registries. In both the Coppo and Hovinga registries, as well as the eculizumab registration trials, aHUS is clearly diagnosed as patients presenting with: (i) evidence of haematological TMA; (ii) TMA-related organ damage; and (iii) no deficient ADAMTS13 activity. This diagnosis is consistent with current medical practice. With regard to the aHUS registries reported in Noris et al. 2010 and Fremeaux-Bacchi et al. 2013, Alexion notes below some of the limitations and assumptions associated with	This is not a factual inaccuracy. The publications reported by Coppo *et al* and Hovinga *et al* are not aHUS-specific registries and the prognoses of patients with other pathologies may not be similar to those for aHUS patients. Noris *et al* and Fremeaux-Bacchi *et al* relate specifically to aHUS patients and this is why we have used these data. This view was supported by clinical advisors to the ERG. It is also noteworthy that much less information is presented on ESRF and mortality outcomes in the Coppo and Hovinga studies than Noris and Fremeaux-Bacchi papers (see ERG report Tables 14 and 15). As noted in the ERG report, the ERG model is exploratory. The ERG wishes to correct the error in the manufacturer's statement - Noris et al did recruit consecutive patients. This is clearly stated in the text. The ERG believes that the aHUS-specific registry data are more appropriate for characterising the prognosis of patients in terms of ESRF

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Fremeaux-Bacchi et al. The ERG also does not acknowledge that both the Noris and Fremeaux-Bacchi cohorts are renal-focused registries that did not enroll consecutive aHUS patients, did not adequately assess other organ damage, and did not follow patients after ESRF. As discussed in the manufacturer's submission (Appendix G, Section D-12.7, p. 175-177) and in the justification for this amendment section, each of these factors could lead to enrolment or survival bias that would underestimate mortality in these cohorts.		these registries for use in modelling disease outcomes. We also highlight the potential impact between our model and the aHUS renal-focused registries to account for some differences in survival analysis outcomes. First, the Noris et al. 2010 and Fremeaux-Bacchi et al. 2013 registries did not enrol consecutive patients as they presented with aHUS, which leads to a potential survival bias in the registry. For example, the Noris et al registry relied on patients voluntarily enrolled by physicians from multiple countries. There is no mechanism in place to ensure consecutive enrolment for all patients. Considering the high and early rate of mortality in patients presenting with aHUS, it can be assumed that most of the patients registered are those with the best survival, leading to a survival bias at study entry. Second, the physicians participating in the aHUS registries also may not have enrolled or followed up with patients with extra renal organ impairment or damage, given that enrolment was limited to renal failure. Therefore, the aHUS registry may select out aHUS patients with mild renal and extra-renal organ damage. Third, once a patient reaches ESRF, it cannot be assumed that mortality is not prevalent as	and death (which are states within the manufacturer's model) than using flawed regression analyses based on the pre-treatment phase of the eculizumab studies. The ERG notes that despite a request for clarification (question 6), the manufacturer has provided virtually no information concerning how patients were identified and enrolled into the prospective eculizumab studies. It is therefore very difficult to draw any firm judgements about comparative risks of potential selection or survivor biases in the registry data and the eculizumab studies.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		chronic dialysis presents a high mortality risk. Noris et al. 2010 and Fremeaux-Bacchi et al. 2013 follow patients to ESRF who require chronic dialysis, but do not capture the high rate of mortality due to dialysis after the short period of follow-up. The overall five-year mortality rate of dialysis patients in 2004 in the United States and Europe is 61% to 65%, indicating generally poor long-term outcomes.(United States Renal Data System 2011; European Renal Association 2011) Further, TMA continues for patients on dialysis and may lead to greater mortality in aHUS patients. Perkins et al (2006) reported that the incidence of TMA in aHUS patients on dialysis was the highest in the first year after aHUS diagnosis and the incidence progresses annually. One-year mortality following a TMA for patients on dialysis is only 42%.(Perkins et al, 2006) Together, this evidence demonstrates that the high mortality rate in dialysis patients is compounded for aHUS patients by on-going complement-mediated TMA in patients receiving supportive care alone . In contrast, both the Coppo et al and Hovinga et al registries present a “real world” expectation of the consistently defined aHUS presentation and outcomes. Both registries present a large sample of “all comers” who are defined by the aHUS diagnostic criteria	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		used to identify patients who would be eligible for eculizumab and currently receive standard of care including PE/PI. These registries include patients from disease onset and follow consecutive TMA patients with any organ damage; they do not limit patients to voluntary patient enrolment by the treating physician. Based on these points, the use of the Coppo and Hovinga datasets is more reliable than use of Noris or Fremeaux-Bacchi.	

Issue 6 <u>Factual inaccuracies in the structure and parameterization of the ERG's model</u>: The ERG's does not consider the effect of children as lower dose/higher life expectancy patients in its analysis.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's report does not consider the effect of children as patients with a lower body weight and background higher life expectancy in its analysis. The ERG states that there are less data to support the use of eculizumab in children; for example, on page 8 of its report: "The evidence base for paediatric populations is comparatively weaker than that for the adult population." However, children form a substantial proportion of the aHUS population, and are part of the EMA-	The ERG should revise its model to include the average patient distribution by age since a large proportion of patients with aHUS are under age 18. By making this revision, the ERG will recognize that younger children need less eculizumab (due to	Clinical trial results submitted for EMA registration resulted in regulatory approval of eculizumab for all aHUS patients, both paediatric and adult. As such, the ERG should consider the effect of children with lower body weight and background higher life expectancy in its analysis. Interim results from an additional prospective clinical trial including 21 paediatric patients are consistent with efficacy and safety of the eculizumab retrospective clinical trials used for regulatory approval, further supporting	This is not a factual inaccuracy. A model for a cohort of 28-year old patients should reflect the expected costs and effects for 28-year old patients, projected into the future. It should <u>not</u> include dose reductions for paediatric patients as 28-year old patients are by definition not paediatric. Had the manufacturer wished to undertake subgroup analyses for paediatric patients, these should have been undertaken in a way which

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
approved eculizumab SmPC for aHUS. The ERG uses a methodological argument to remove children from the manufacturer's model, namely that health state models such as the one submitted by the manufacturer consider only cohorts identical individuals. This argument has some merit, but as included in the manufacturer's October response document answering the ERG's questions, the full age distribution of indicated patients was modelled, and a proportion of aHUS patients below age 18 were assumed, as this is what is seen in medical practice. A microsimulation would have been a more precise way of including children as a part of the base case complete distribution of aHUS patients, but we did not have time to complete such an analysis. The manufacturer's existing model likely produces similar results.	weight-based dosing), yet gain more QALYs due to a greater background life expectancy. Ideally, the ERG should model an average cohort as in the manufacturer's submission (or proposed in its response document), or conduct a microsimulation of patient ages. However, at minimum, the ERG should address this point in a sensitivity analysis and update its report accordingly.	efficacy and safety in paediatric patients (manufacturer submission, Appendix G, Section C-9.4.4 and 9.9.1). Therefore, the value of eculizumab should be considered for the entire patient age distribution. QALYs increase more rapidly than do costs in a younger patient population, and excluding them biases the model against eculizumab.	reflects the costs and outcomes applicable to that subgroup. The ERG did not undertake a separate subgroup analysis for children as new subgroup analyses were beyond our remit. We are not responsible for the absence of economic evidence in this subgroup. The ERG notes that evidence for the paediatric population is limited and it would be difficult to fully examine heterogeneities in risks of CKD damage for patients receiving eculizumab or standard care. The economic evidence available is thus insufficient to determine whether results would be similar or different for children and adults.

Issue 7 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG misrepresents the causes of the differences between its model and the manufacturer's model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG misrepresents the differences between its model and the manufacturer's model (in particular, see Issues 8-10 below). On page 106 of the ERG's report it states: "The ERG critique identified several problems relating to the manufacturer's cost-consequence model. The most important of these concerns relate to the restrictive structural assumptions of the model, the inappropriate interpretation of evidence relating to the benefits of eculizumab over time, the inappropriate use of evidence to characterise CKD damage for patients receiving standard care, the inappropriate method for handling competing event risks and the highly questionable choice of relevant evidence used to characterise the prognosis of patients receiving standard care. Whilst some of these problems could be resolved easily within the existing model, other more serious programming issues cannot not be resolved within the manufacturer's model structure (in particular, the inappropriate approach used to handle competing risks)." However, after reviewing, it appears as though none of these issues is meaningful	The ERG should adjust its model based on the prior six issues described above. Upon doing so, it should then revise its report on page 106, given that its revised model would then be quite similar to the manufacturer's model after these changes are made.	The justification for this change is based on two factors: First, if the prior six issues are corrected in the ERG's model, its model would produce similar results to that of the manufacturer's. (Please see attached a corrected version of the ERG's model with red highlighting of cells that have been modified to address the prior six issues described above.) Second, the critiques the ERG makes of the manufacturer's model have minimal impact on model results once revised.	This is not a factual inaccuracy. The ERG model rectifies the structural problems in the manufacturer's model whilst remaining as close as possible to it. The ERG would suggest that whether a problem has an impact on the model results or not does not influence whether the problem exists. The ERG agrees that there were two technical errors in the ERG exploratory model (see response to point 2). We have rectified these and they do not have a material impact upon the incremental results. The other issues purported to be errors by the manufacturer, are not errors. The difference between the results of the ERG model and the manufacturer's model remain substantial.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
to the difference in results between the manufacturer's model and ERG's model. It is inaccurate for ERG to indicate that the above reasons causes the difference between the two models, when in fact the biggest difference between the two models is due to the errors in the ERG's model described in Issues 1-6 above. After addressing and correcting for these errors, the incremental life years gained in the ERGs model increase by 25.14 and incremental QALYs gained increase by 20.50 in the ERG's model, bringing the results close to the manufacturer's model.			

Issue 8 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG states that the manufacturer's model's structural restrictiveness with regard to eculizumab is a major concern, but the ERG's recommendation modifications have an extremely small impact on the results.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on page 101 of its report: "the ERG has concerns with respect to the restrictive nature of the manufacturer's model structure." The ERG's main point has to do with its premise that the Markov traces should be	The ERG should make clear that its recommended approach to eculizumab modelling leads to essentially the same	The ERG's comments are misleading and could be construed inappropriately to mean that there is a substantial difference in the manufacturer's model and the ERG's model with regards to model structure, when in fact a large discrepancy does not exist.	This is not a factual inaccuracy. The manufacturer's model is restrictive as it includes a single transition matrix which means that time-dependent event risks cannot be considered within the model structure. The results of the

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
time varying. Markov models are by definition memoryless, and do not condition future likelihoods on past state transitions. In other words, the manufacturer's modelling approach is consistent with standard practices. For example, in Briggs, Andrew Harvey, Karl Claxton, and Mark J. Sculpher. *Decision modelling for health economic evaluation*. Oxford University Press, 2006, such a memoryless Markov model is described to model HIV in a sample containing almost 5,000 transitions (Chancellor et al., 1997). Given that the manufacturer's model—based on data from the C08-002 and C08-003 clinical trials—has only 211 transitions, Alexion thought it is empirically sound to be parsimonious and not make assumptions about the relationship of time to the transitional probabilities. The factual inaccuracy in the ERG's report is that the approach that the ERG takes, with regard to eculizumab modelling, leads to modestly different results (e.g., page 106), despite stating that the model's restrictive structure is problematic. The ERG's model results in similar (even larger) QALYs and life years for eculizumab compared to the manufacturer's model. Further, the ERG assumes that the model's transition in cycle 7, for which the fewest	results as the manufacturer's model and that the manufacturer's model structure is not inappropriately restrictive.		ERG model are not similar to those produced by the manufacturer. The ERG draws attention to Figure 6 and Figure 8 in the ERG report. The ERG method fits the data closely as it is based on the actual observed transitions within the trial. The manufacturer's method (Figure 6) fits the data less well and is likely to produce an unnecessary bias in the modelling of the eculizumab arm. This does have an important impact on the long-term survival and QALY gains for patients receiving eculizumab. In addition, the ERG have examined the impact of alternative extrapolation assumptions on model results; there is little more that can be done in the absence of longer-term data. Based on the data from the two aHUS registries, the evidence suggests a high risk of ESRF/death in the short-term but a lower risk in surviving patients. This would suggest time-dependence. The manufacturer's model does not allow for this time-dependence.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
observations are available, continues to perpetuity. This is a stronger assumption than that used in the manufacturer's model write-up, given that there are fewer observations by cycle 7, but patients are presumed to continue in the model for the next several decades only based on the observations in this cycle.			

Issue 9 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG states that competing risks are a major issue, noting only an extreme case for a highly improbable situation.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section "(5) Inappropriate handling of competing risks" on page 102 of its report, the ERG writes: "For example, in the eculizumab group, if the excess death risk for patients in ESRD is arbitrarily inputted as 0.80 (cell X13 markov_ecu worksheet), the probability of remaining in ESRD becomes -0.377. This is mathematically impossible and raises further questions regarding the robustness of the manufacturer's model results." The ERG means that the model "breaks" if a user changes the base case and assumes that 80% of eculizumab-treated patients die in one six-month interval. In fact, any value	The ERG should remove the statement reference from its report.	The scenario the ERG uses to justify its comment is disconnected from the actual observations and data seen with eculizumab in aHUS, on which the manufacturer's model was built. Considering that there has been only one death in all eculizumab trials (C10-003 and C08-004, and up to 3.5 years exposure time for in C08-002 and C08-003, for a total of 392 six-month periods, yielding a six-month death rate of 0.26%), a 42.3% chance of patients dying, as outlined in the ERG scenario, seems unnecessary. The model could be amended if a greater rate of death is observed.	This is not a factual inaccuracy. If changing a probability parameter leads other transition probabilities to turn negative, as is the case here, there is unequivocally an error in the model. The fact that the data estimates used in the model are not large enough to produce the error is irrelevant. It is still an error, and if it cannot be resolved, the model should be interpreted with considerable caution.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
over 42.3% of patients dying in one six-month period would "break" the model. However, such a scenario is not consistent with the data, given that there has been one death in the C08-002, C08-003, C10-003 and C10-004 trials over a total of 392 modeled six-month periods, yielding a six-month death rate of 0.26% (1/392), which is less than 1% of 0.423. The death was determined not to be related to the study drug. In other words, the rate of patients dying would have to be more than 100 times greater than it has been observed to be for such an outcome to occur. Accordingly, we did not develop the model to handle such an anomaly. If a higher mortality rate had been observed in the trials, we would have programmed the model differently, but due to the low mortality rate, the model created was the most reasonable.			

Issue 10 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG engages in speculation about the EQ-5D data, which are refuted based on the HRQoL scores provided from the eculizumab trials.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 101, the ERG speculates about	The ERG should	The ERG engages in speculation about how	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the EQ-5D data reported in Legendre et al., *New England Journal of Medicine*, 2013: "However, given the absence of randomisation and blinding within the prospective eculizumab studies, the considerable expense of eculizumab, and the absence of an alternative effective treatment for aHUS, it is possible that some patients valued their health on treatment because they were receiving eculizumab rather than because the drug had a noticeable impact upon the patients' HRQoL." This speculation is not based on empirical research of which Alexion is aware. Specifically, Alexion is unaware of any empirical evidence to date, in the form of a health utility analysis (e.g., time trade-off) or a study of preferences (e.g., discrete choice experiment), where patients indicated a preference for a technology solely because it was expensive. The ERG does not cite such evidence in their report so the source of its argument is not known.	remove the statement on page 101 from its report.	the health utility gain for eculizumab could be lower than it is reported in the trials. No evidence is provided in support of this conjecture. As noted in the manufacturer's October 2013 response to the ERG's questions, Alexion is unaware of any empirical evidence to date, in the form of a health utility analysis (e.g., time trade-off) or a study of preferences (e.g., discrete choice experiment). Also in Alexion's October response document addressing the ERG's requests for additional information, in the answer to question 53, the HRQoL scores by week are presented. Because patient HRQoL does not peak until week 4 or later, the ERG speculation could only be true if patients learned how expensive the drug was at or after week 4. The slope between week 0 and this time point would have to be interpreted as the patient's gradual learning about the drug's expense, which it is not.	It is speculation and is stated as such in the ERG report. The absence of a control group may have introduced bias. It is not unreasonable to raise concerns about the manufacturer's assumption that patients in the same health state receiving different treatments will have such different levels of HRQoL. This is an uncertainty due to the lack of evidence and is recognised as such within the ERG report.

Issue 11 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG misquotes the manufacturer's report about missing data imputation, and then speculates how their misconception could affect results.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG misquotes text in the manufacturer's report about missing data imputation for patients on dialysis, then goes on to speculate how results could be affected were this misconception actually true. On page 92 of its report, the ERG states that "The manufacturers state that for *<u>any</u>* missing data, eGFR measurements are assumed to take a value of 10; however, this seems an arbitrary choice…" (manufacturer's emphasis.) The ERG goes onto speculate that "The graph of the applied LOWESS regression indicates a considerable amount of missing data (the data suggest a lot of values of eGFR=10); this crude imputation approach may skew the results of the regression models. It would have been preferable to explore scenarios in which a more sophisticated multiple imputation approach was used and no imputation." In fact, the ERG misread the manufacturer's submission, and created a false premise that Alexion imputed a	The ERG should remove the statement on page 92 from its report.	Patients not on dialysis do not have imputed scores, as is clearly described in the text in the manufacturer's submission (Appendix G).	This is a minor discrepancy over wording. The text has been changed from "any patients" to "patients receiving dialysis." The evidence in the submission did not justify the choice of the imputed value and is thus not factually incorrect.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
substantial amount of missing data when that is not the case. As stated on page 143 of the manufacturer's submission (Appendix G), a limitation of the manufacturer's analysis is as follows: "Third, most patients *on dialysis* do not have eGFR measurements. In these cases, measures were imputed to be "10", so there is a higher "floor" or minimum value for many patients in ESRF." Patients on dialysis often do not have their eGFR measured, given that their kidneys no longer function. These missing eGFR data were imputed to be 10 for patients on dialysis, based on suggestion of peer reviewer comments from reviewers at the *New England Journal of Medicine*. In short, patients not on dialysis do not have imputed scores in the manufacturer's model and the ERG does not note how this imputation biases the days-eGFR estimation upward in the regression analysis.			

Issue 12 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG incorrectly describes the manufacturer's random effects model with a trial dummy specification then suggests an incorrect specification to address the issue.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 92 of its report, ERG states that "The second mixture model (model c) attempted to take into account that the data were drawn from two studies by including a dummy variable, although this is not handled appropriately. The model yields a common coefficient, β, for the number of days and the trial indicator variable, which adds an extra day to the number of days before baseline if the data arises from one of the two trials… A more appropriate model specification would thus be: $eGFR_t = \alpha + \beta_1(days_{it}) + \beta_2(trial_{it}) + u_{it} + e_{it}$." The ERG's critique of the manufacturer's random effects model is incorrect. Alexion clearly indicates that a specification with a trial dummy is used on page 142 of the manufacturer's submission. Nothing in the manufacturer's submission supports the interpretation that a model that "yields a common coefficient" was included. Alexion believes that the ERG misread the second column header from Table D3: eGFR decline per day in the pre-treatment period in patients receiving SOC, which clearly reads "Coefficient on days (β)".	The ERG should remove and/or correct the statement from page 92 of its report.	The ERG did not read the manufacturer's description of the random effects model with a trial dummy variable specification carefully; Alexion indicates the correct specification in the original manufacturer's submission document (Appendix G).	The ERG believes that even if the manufacturer has undertaken the analysis correctly, the model specified in the submission is written incorrectly. The manufacturer's specification of model (3) is as follows: egfr_it=α+ β(days)_it+β(trial)_it+u_i+e_it However, this would simplify to: egfr_it=α+ β(days+trial)_it+u_i+e_it As the trial variable is a dummy variable, suppose it takes the value of 0 for trial 1 and 1 for trial 2. The model is therefore as follows for trial 1: egfr_it=α+ β(days)_it+u_i+e_it, where β is the coefficient for the number of days. However, for trial 2, the model takes the following form:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is also clearly stated on page 142 of the manufacturer's submission (Appendix G) that the manufacturer's third model specification is: $egfr_{it} = \alpha + \beta(days)_{it} + \beta(trial)_{it} + u_i + e_{it}$. In fact, the specification the ERG suggests is incorrect, as it has the "u" and "e" error terms both varying across "i" patients and "t" time when only "e" varies across patients and time and "u" only varies within patients (i.e., u_i not u_{it}).			egfr_it=α+ β(days+1)_it+u_i+e_it, now β is the coefficient for the number of days+1. This is not reflected in Table D3. By the model specification, the manufacturer is assuming that the coefficient is identical for the number of days and the trial under observation. However, there was a typing error with regards to the indices which should be amended in the report. The ERG agree that there is an error in the suggested re-specification. We have amended this in the final report.

Issue 13 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG claims that the manufacturer's fixed effects model is wrong without evidence and misquotes the manufacturer's description of the fixed effects model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 92 of their report, the ERG states: "The manufacturer's interpretation of a fixed effects model (model d) seems to be	The ERG should remove this statement from	Our model specification was a correct use of fixed effects. This is consistent with common econometrics, for example, JM	There is a misunderstanding of the fixed effects model by the ERG. The ERG however believes that the

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
incorrect". However, the ERG does not provide evidence to support its claim. In fact, this seems to be a misunderstanding, as the manufacturer's model is correct. The manufacturer's STATA code was: xtreg egfr adyx if adyx<1, i(subjid_n) fe The "fe" command at the end of the procedure line specifies a fixed effects specification. See STATA, v13; xtreg, options. Alexion also did not state that the "fixed effect model enables patient characteristics to be removed". Rather, on page 141, Alexion states patient characteristics are "demeaned, meaning that the average time invariant effects are controlled for each patient. Static patient characteristics, such as observables like patient race or unobservable characteristics like the patient's (static) genetic propensity to suffer from aHUS, are removed as sources that could bias β, which is the change in eGFR per day on SOC." This is a correct description of the procedure. Note that differences in the trials also are controlled for with the correct use of fixed effects.	page 92 of its report.	Woolridge, *Introductory Econometrics*. Thomson, Southwestern, 2003.	description of the model in the manufacturer's submission was not clear. Given the additional information presented in this document, the ERG accepts the proposed solution.

Issue 14 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG suggests the wrong model test for assessing which model specification should be estimated.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 92 of the ERG report, the ERG states that "The manufacturer does not report any form of formal model checking to assess the suitability of any of the four regression models. The ERG believes it would be appropriate to produce diagnostic plots and/or Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values to assist with model selection." Although these tests suggested by the ERG can have value, given that Alexion was asked to model expectations, and that a limited sample exists, the AIC and BIC tests would not be informative about which specification to use. Given that data from 37 patients does not allow sufficient statistical power for multiple covariates to be included, specifications are not an issue, though model functional form is. A correct model test would distinguish between the fixed effects and random effects models. The correct econometric test to achieve this would be the Hausman test (i.e., Durbin-Wu-Hausman test), but this test is irrelevant because the RE and FE coefficients were the same, and the model operates on coefficients.	The ERG should remove this statement from page 92 of its report.	The correct econometric test would be the Hausman test, but this test is irrelevant because the RE and FE coefficients were the almost the same, and the model operates on expected values so uses the coefficients. The manufacturer also uses LOWESS to assess linearity, which is another way in which the regressions were assessed as valid for a prediction model.	This is not a factual inaccuracy. The manufacturer even suggests that there would be value in undertaking these tests. This suggestion is not included in the MS.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Additionally, the ERG's statement that: "The manufacturer does not report any form of formal model checking to assess the suitability of any of the four regression models" is factually not true. The manufacturer uses LOWESS to assess linearity nonparametrically.			

Issue 15 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG incorrectly states that Alexion pooled trial data in all analyses.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 92 of its report, the ERG states that "This OLS model, the first mixture model (random intercept, fixed slope) and the fixed effects regression model (models a, b and d) each use pooled data from both trials which implicitly assumes that the two studies, and the patients recruited into them, are identical." This is not true—in specification (3), Alexion includes a dummy variable controlling for trial, correctly specifying the effect (see page 141 of the manufacturer's submission (Appendix G). Additionally, in the fixed effects regression, since the trial into which a patient was randomized is time invariant, Alexion	The ERG should remove this statement from page 92 of its report and note that Alexion controls for trial differences in specifications (3) and (4).	As noted in the manufacturer's submission, controls for trial differences in specifications (3) and (4) were implemented. A univariate sensitivity analysis also looked at results for the different samples independently.	The ERG has recognised that model (3/c) in the manufacturer's submission does attempt to adjust for the trial variable and so we only suggest that models a, b and d don't adjust for trial identity. We agree that the fixed effects model controls for the patient-specific time-invariant effects, however, it does not adjust for trial-specific effects.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
controls for the differences in trials again in this specification (see page 141 of the manufacturer's submission (Appendix G). A univariate sensitivity analysis also looked at results for the different samples independently.			

Issue 16 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG includes a note that "not all transitions are allowed for standard care", which is not correct.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 80 of its report, the ERG states: "**note – not all transitions are allowed for standard care*". The manufacturer's model handles transitions of eculizumab and SOC in a symmetric way. The Markov matrices are identical. Alexion parameterized all inputs with data from the C08-002 and 003 trials. Inputs vary in the two models, which is a function of the data.	The ERG should remove this statement from page 80 of its report.	The Markov matrices are identical, which disproves ERG's comment.	This is not a factual inaccuracy. If a model structure includes a transition but that transition is fixed at a value of zero, the transition is not allowed. The manufacturer's model does not allow CKD improvements for the standard care arm whilst the eculizumab arm does. Transplants are not allowed for patients receiving eculizumab even though a patient did undergo transplant in the studies. Patients receiving eculizumab cannot die of aHUS whilst those receiving standard care can.

Issue 17 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG states there is an error in the manufacturer's SOC model related to boundedness, based on an extreme scenario, which is not based on data.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 94 in its report, the ERG states that "In their response to clarification (question #32) the manufacturer stated 'The boundedness issue is only a problem when we are close to 0% or 100%. In our case, it would require 12 times the standard error to reach the lower bound and 20+ times the standard error to reach the upper bound—which are likelihoods that are vanishingly small given the data.'" The ERG believes that the fact that the probability does not exceed 1 is irrelevant; the issue is that it *could do* and the manufacturer's approach is not estimating a transition probability."(The ERG's emphasis.) This comment is reasonable in a pure mathematical sense; however, given the data available, the event is extremely unlikely (i.e., there is less than a 0.0000000001% chance of this occurring). The ERF.PRECISE function in MS Excel 2010 is incapable of measuring the probability of an event more than 7 standard deviations from mean, as it is so rare.	The ERG should remove this statement from page 94 of its report.	The model should not be required to allow for events occurring at a probability of below 0.0000000001%.	This is not a factual inaccuracy. The manufacturer even notes that our comment is reasonable. Fitting a linear unbounded model to estimate probabilities may produce highly erroneous results. It would have been advisable to consider alternative analyses to estimate these parameters.

Issue 18 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG notes a discrepancy in the manufacturer's description of the pretreatment period, but then inappropriately calls into question the manufacturer's entire data analysis as a result.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG reasonably points out that Alexion has included inconsistent figures on the duration of the pretreatment period; however, this inconsistency was a minor mistake and is easily corrected. The entire results of the manufacturer's analysis should not be discarded because of this typographical error. The ERG states on page 105 of its report: "The ERG also is unclear regarding which patients were included in the pre-study population analysis…," pointing out that Alexion has included (inadvertently) different figures in Table C8 and in the description of the pretreatment period model. While the ERG is correct and makes a good point, the ERG goes on to state on page 95 that "The exclusion of either patients with long standing aHUS or observations from earlier in their disease process may bias the results of the regression analysis." It does not follow that the manufacturer excluded patients or dropped observations in the analysis. The ERG goes on to write in its report that	The ERG should revise its report to not speculate that observations were dropped in the manufacturer's model for the eGFR pretreatment period. Instead, the ERG should acknowledge that a typographical error was made in the manufacturer's report.	Alexion's clarification that the pretreatment period in the SOC model begins with the first eGFR measure is consistent with the rest of the section on page 140 of the manufacturer's initial submission (Appendix G), where all eGFR measures in the pretreatment period are discussed. In addition, the ERG did not ask for clarification of the pretreatment period in its October request for additional information so Alexion presumed the explanation given in the manufacturer's submission was sufficient.	It is not entirely clear from the manufacturer's description of the problem where the typographical error occurred. The ERG has interpreted the error as an error in the definition of the pre-treatment period. In the MS the pre-treatment period used to estimate the standard care transition probabilities was mistakenly referred to as being from diagnosis to baseline when it should have been referred to as being from first eGFR measurement to baseline. Therefore the data presented on P140 of the MS are correct and represent first eGFR measurement to baseline, and the data in Table C8 correctly represents time from diagnosis to baseline. If the ERG has interpreted this correctly, then we still have concern over this analysis. The manufacturer has not explained why there is such a delay between diagnosis (Table C8)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the "MS states that 'the pre-treatment period was defined as the time from diagnosis to baseline in the trials' (MS1 page 140)." Alexion acknowledges that this should have been written as "the pre-treatment period was defined as the time from diagnosis and **first eGFR measure** to baseline in the trials" (new text in bold) and apologizes for the omission. It should be pointed out that the complete section reads: "The pre-treatment period was defined as the time from diagnosis to baseline in the trials. The two trials combined contained 1,847 eGFR pre eculizumab treatment observations. The median interval between diagnosis and baseline was 186 days with a range of (965, 1) and interquartile range (IQR) of (334, 67). In the pre-treatment period, eGFR observations per patient average (min/max) 31.2 per patient (1/108). Note that prior to the screening period, these observations were collected retrospectively for enrolled patients." That is, the manufacturer was discussing a model based on eGFR measures, and characterized the pretreatment period based on those measures. Alexion also would note that the ERG did not ask for clarification of the pretreatment			and the first eGFR measurement taken (data P140). This delay is not only evident in Table C8 but is also evident in the time to transplant shown in Figure 5 in the ERG report. This shows that the one of the transplant patient was diagnosed over 250 months before baseline and their first transplant occurred at about 250 months before baseline. According to the data on P140 of the MS, the median interval between first eGFR measurement and baseline was 186 days with a range of (965,1). Given these data, it seems surprising that a patient with diagnosed aHUS and undergoing three renal transplants would not have an eGFR measurement taken for over 17 years which is the ERG's interpretation of the evidence given the manufactures explanation. Therefore the ERG is still concerned that no explanation is given as to why there is such a delay between diagnosis and the first eGFR measurement being taken and that the potential bias that might arise from this discrepancy is not mentioned or explored in the MS. Irrespective of the lack of clarity in the

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
period in its October request for additional information so Alexion assumed the ERG accepted the explanation given. Alexion also thinks it is inappropriate that the ERG speculates that observations were dropped when in fact no pretreatment period eGFR observations were dropped.			MS concerning this point, the ERG does not believe that these pre-treatment data are appropriate for informing the standard care arm of the model.

Issue 19 <u>Factual inaccuracies in the description of the manufacturer's model or documentation</u>: The ERG identifies minor technical errors in the manufacturer's calculations, but does not indicate the effect of these on results; had the ERG incorporated these corrections, the results only would have changed by less than 0.5%.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG correctly identifies a few technical errors in the manufacturer's model including page 96-97: "Problem 7: Issues relating to the calculation of the probability of undergoing transplant" that the transplant rate was not correctly counted; page 104: "the sum of standard care transition probabilities greater than 1.0" for the transition out of kidney transplant; a mis-linking of inputs, but acknowledges that this issue does not affect the base case output of the manufacturer's model; and a point about double discounting about which	The ERG should acknowledge that the technical errors identified in the analysis, while correct, do not have a material effect on the model outcome.	Without acknowledging that the errors identified in the analysis do not have a material effect on the model's outcome, a reader could be misled that the manufacturer's model is not valid, or at least substantially more valid that the ERG's model, for which is illustrated above has serious technical flaws.	This is not a factual inaccuracy. The manufacturer notes that the ERG is correct. The impact of resolving minor technical errors on the manufacturer's model is already reported in Table 35 of the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Alexion disagrees. Alexion thanks the ERG for bringing these issues to its attention; however, these errors have an extremely small impact on the final results. Modifying all of these issues would change the ICER, had one been calculated, by less than 1%.			

Issue 20 <u>Factual inaccuracies related to systematic review, clinical data, and interpretation of decision problem</u>: Completeness of systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that it "is not convinced that all available evidence on the comparators in the MS has been systematically identified, quality assessed and the outcomes fully reported…" (Section 1.3, p. 2, and similar statements repeated throughout the report). Identification and systematic review of studies including comparators, but not comparing them to the technology under assessment, is not requested under the NICE HST specifications and therefore was not included in the manufacturer's	Any critique describing the systematic review of comparator studies should be removed from the ERG's report as this is not applicable to the specifications and direction given by NICE. Additionally, the ERG's report	This critique from the ERG demonstrates a fundamental disconnect between the independent review methods performed by the ERG and the requirements for the submission defined by NICE. In addition, it assumes Alexion did not pursue due diligence when in fact the comparator studies requested by the ERG do not exist. The NICE HST specifications for submission of evidence clearly state that sponsors are required to "present published and unpublished clinical evidence **for [the] technology**" (Appendix G HST INTERIM evidence submission template,	This is not a factual inaccuracy. The ERG critique highlights that a systematic review of the comparators was unlikely to have been undertaken based on the information provided in the MS and the manufacturer's clarification response. It is noteworthy, that the manufacturer now states that an 'independent systematic review of the comparator only studies was not conducted for the reasons described above' and considers this to be a *'…typographical error...'* The ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
submission.	should be updated to indicate there are no studies comparing the noted comparators to eculizumab.	July 2013; Section C-9, p 19) and that "details of all published and unpublished studies **that compare the technology with other treatments for the relevant group of patients** should be presented…" (Appendix G HST INTERIM evidence submission template, July 2013; Section C-9.3.1, p 23). There is no requirement in the evidence submission specifications for identification of published or unpublished studies which include the "comparators" but do not include a direct comparison to the technology under evaluations. Accordingly, no studies that included the comparators alone would be identified in the search conducted according to the NICE specifications. Therefore, Alexion believes that the critique regarding the lack of systematic review of comparators as well as the ERG-conducted systematic review is not appropriate to include in the report because they are not relevant to the requirements set forth by NICE. Alexion maintains that the submission has fulfilled specifications set forth by NICE, as acknowledged in the report that the "ERG is confident that all relevant studies (published and unpublished) of eculizumab were included in the MS, including data from ongoing studies."(ERG Report, section 4.5.1, p 62) The manufacturer's submission clearly states that there were "no studies identified that compare the intervention	notes that the response from the manufacturer provided at clarification (question 1), presented in italics below, is not simply a typographical error. *"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 ESRF, dialysis, and early mortality.* • *Alexion Submission Page 31: "The disease affects both children and*

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		with relevant comparators" (Appendix G, section 9.3.1, p 66) as specified by the submission template which indicates that "The studies that compare the intervention directly with the appropriate comparator(s) referred to in the decision problem should be clearly highlighted. If there are none, please state this." (Appendix G HST INTERIM evidence submission template, July 2013; Section C-9.3.1, p 23) However, the manufacturer's submission does include discussion of the comparators defined in the scope elsewhere in the submission. As described in the rationale for variation from scope, "Current data available and actual clinical practice do not allow this information to be presented in the distinct groups described in the final scoping document…"(Appendix G, Section A-1, Table A1, p. 21) The comparators defined in the scope are limited supportive care options used in clinical practice that are not indicated or designed to directly treat aHUS, and there is no controlled evidence demonstrating that supportive care can alter the course of disease. Therefore, these options cannot be directly compared to the eculizumab evidence presented in the submission. The issues relating to the use of these supportive care options are described further in the manufacturer's submission (Appendix G, Section B-8.3, p. 51).	*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.]*

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		Also as noted in the manufacturer's submission, the authors of the eculizumab clinical trials noted that the significantly lower rate of interventions including PE/PI and dialysis highlight the inadequate efficacy of management with PE/PI and confirm the clinically relevant treatment effect of eculizumab on TMA and organ outcomes, with a striking improvement in renal function upon discontinuation of PE/PI and initiation of eculizumab (Appendix G, Section C-9.8, p. 109). Separately, Alexion would like to acknowledge an inaccurate statement that was unintentionally submitted in response to the ERG's request for clarification received on October 4, 2013. As noted in the ERG report, it was incorrectly stated in response to question #1 that a systematic review of the comparators was provided (ERG report, Section 3.3.3, p. 23). In fact, an independent systematic review of the comparator only studies was not conducted for the reasons described above. Alexion apologizes for this typographical error and requests that it be corrected and marked as such for the record. The remainder of the response to this request for clarification is however accurate in referencing the discussion of four key TMA registries and the outcomes associated with	• *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."* • *Alexion Submission Page 139: "The Coppo and Hovinga datasets consist of adults with confirmed*

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		supportive care (comparators relevant to the scope) that are described elsewhere in the submission.	*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."*

Issue 21 <u>Factual inaccuracies related to systematic review, clinical data, and interpretation of decision problem</u>: Clinical trial evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG inaccurately characterizes the relevancy and certainty of the eculizumab clinical trial outcomes and their impact on longer-term, patient relevant-outcomes, including ESRF and survival, stating that "The prospective and retrospective studies of eculizumab discussed in the MS are relatively short-term and focus on intermediate endpoints. Whilst these endpoints are clinically relevant, their translation to longer-term patient-relevant outcomes (e.g. survival) is subject to	The ERG's report should be modified throughout to recognise the impact and relevance of the reported outcomes on long-term renal function and survival.	While Alexion agrees with the ERG that the endpoints are intermediate outcomes, it is clear and with a high level of certainty, that renal function in particular is an evidence-based outcome that is translatable to longer-term patient-relevant outcomes, including ESRF and mortality. The outcomes chosen for the eculizumab clinical trials were extensively reviewed and accepted by regulatory agencies, expert physicians, and peer-reviewed publications.	This is not a factual inaccuracy. We have not said they are not relevant outcomes, and as pointed out by the manufacturer in their response, we have said the exact opposite. There are no long term studies of eculizumab on survival. Translating an intermediate endpoint to longer-term outcomes is thus subject to uncertainty.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
considerable uncertainty." (Section 9.4.2, p. 138)		The uncertainty expressed by the ERG demonstrates a lack of understanding the progression of kidney disease in aHUS and its impact on patient survival, as described in the manufacturer's submission (Appendix G, Section D-12.2.1, p. 144; Section D-12.7.1, p. 175) As quoted in the manufacturer's submission and the ERG's report, 33-40% of aHUS patients die or progress to ESRF with the first aHUS clinical manifestation, despite the use of PE/PI in the vast majority of these patients. However, the ERG report fails to recognize the unquestionable evidence presented in the manufacturer's submission from large and well-resourced UK and US renal disease databases describing the survival of ESRF patients. While there is no well-controlled aHUS-specific data describing this progression from ESRF to death, it is reasonable to assume that this progression is similar to that of the general ESRF population. This reasoning is incorporated in the justification of the use of the renal registry survival data for the SOC arm of the cost-consequence model presented in the manufacturer's submission. The primary goal of therapy in aHUS is to halt disease progression and TMA-mediated organ damage. The outcomes chosen for the clinical trials clearly demonstrate the ability of	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		eculizumab to achieve this treatment goal by improving or stabilising renal function. Disease progression in patients receiving supportive care including PE/PI is demonstrated in the eculizumab clinical trial population by the large proportion of patients with significant renal impairment including progression to ESRF prior to eculizumab treatment. As described by Legendre et al 2013, this pre-treatment data serves as within-patient control. The improvement in renal function and lack of progression to ESRF with eculizumab compared to the pre-treatment period demonstrates the ability of eculizumab to alter the disease process, having a significant impact on patient-relevant outcomes. The improved survival and lack of progression to ESRF in eculizumab-treated patients compared to aHUS and TMA registry aHUS patients receiving supportive care demonstrates the translation of the intermediate renal outcomes to long-term outcomes including ESRF and survival.	
The ERG report disregards its stated remit for its report to evaluate the benefits and costs of eculizumab within its licensed indication, speculating that "There exists no published evidence on alternative dosing to that described in the license or on the use of intermittent treatment to manage flares. As aHUS may follow a relapsing/remitting type of disease course for some patients,	The ERG should remove speculation from its report on modification of eculizumab dosing outside of the licensed indication of for aHUS.	As described in the ERG report, "The remit of this appraisal, as defined in the final agreed NICE scope, is to evaluate the benefits and costs of eculizumab within its licensed indication for the treatment of aHUS for national commissioning by NHS England."(Section 3.1, p 19) The approved dose and dosing regimen for eculizumab was demonstrated to be effective in clinical trials	This is not a factual inaccuracy. The ERG critique highlights that there are uncertainties in the optimal dosing of eculizumab. In addition, despite the SmPC recommending lifelong treatment, the ERG highlight that current practice at the national aHUS centre in Newcastle (led by Professor

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
continual use of eculizumab may not be necessary once the patient has stabilised (the same is true of plasmapheresis in a proportion of patients)." (Section 1.10, p. 8) In addition, the ERG states that "the current interim national service for aHUS in Newcastle, implemented by NHS England, considers withdrawing (or restarting) eculizumab therapy based on a set of criteria that depend on the patients circumstances" and cites aHUS Action physician group submission (Section 4.5.3, p.64). However, the ERG neglects to acknowledge that this opinion described by the physician group is not within the licensed indication of eculizumab for aHUS and is not recommended under the current NHS England Clinical Commissioning Policy Statement.	Specifically, the ERG should correctly state in its report that NHS England's commissioning document indicates lifetime eculizumab treatment is aligned with the approved SmPC. The ERG should also amend its report to indicate the UK physician group's considerations of eculizumab withdrawal are not within the licensed indication of eculizumab aHUS and beyond the ERG's remit. Finally, the ERG should remove all references to alternative eculizumab dosing from its report.	and approved by regulatory authorities within the licensed indication. Speculation about alternative dosing schedules is not based on any clinical data and is outside of the remit of the ERG's scope and assignment. The SmPC indication as well as the current NHS England Clinical Commissioning Policy Statement for eculizumab for aHUS state that life-long treatment with eculizumab is necessary, citing disease risks with treatment discontinuation. The speculation of the ERG that continual use of eculizumab may not be necessary demonstrates a lack of understanding by the ERG of this ultra-rare disease and constitutes an attempt to evaluate the benefits of eculizumab outside of its licensed indication. Meanwhile, the ERG's citation of the physician group submission as considering conditions for eculizumab withdrawal are not aligned with the licensed indication and not recommended under the current NHS England Clinical Commissioning Policy Statement. Nevertheless, the ERG itself states in its report that "there exists no published evidence on alternative dosing to that described in the license or on the use of intermittent treatment to manage flares." (Section 1.10, p. 8) As described in the manufacturer's submission, aHUS is a chronic, life-long	Tim Goodship), does not consider lifelong eculizumab treatment for all patients but considers withdrawing (or restarting) eculizumab therapy based on a set of criteria that depend on the patient's circumstances.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		disease due to genetic mutations in the complement system. Historical views of aHUS as an intermittent disease were likely based upon measurable levels of thrombocytopenia and haemolysis that may fluctuate during the course of disease. However, as demonstrated by the eculizumab clinical trials and Legendre et al, 2013, patients with platelet levels within normal range are not “stable” and still have manifestations of complement-mediated TMA including renal impairment and ESRF. Furthermore, it is factually inaccurate for the ERG to state that there exists no published evidence on alternative dosing in aHUS since as described in the manufacturer’s submission, a number of patients in the prospective and retrospective eculizumab trial that discontinued eculizumab, or did not receive indicated dosing, experienced severe TMA complications (manufacturer’s submission, Appendix G, Section C-9.7.3, p. 107-109). These events led to the inclusion of a safety warning in the SmPC describing the risks and monitoring for TMA complications in the event of discontinuation. In addition to this clinical trial evidence, a number of published case reports describe TMA complications and disease progression, including irreversible end-organ damage (Appendix G, Section C-9.9.3, p. 117), when patients discontinue eculizumab treatment.	

Issue 22 <u>Factual inaccuracies related to systematic review, clinical data, and interpretation of decision problem</u>: The ERG did not follow NICE's instructions related to including ICERs and referencing past submissions.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
NICE explicitly instructed both the ERG and Alexion at the scoping meeting and during a follow-up teleconference that incremental cost-effectiveness ratios (ICERs) should <u>not</u> be included. Despite these instructions, the ERG begins Section 5 of its report by suggesting that NICE use ICERs to evaluate UODs and continues to report ICERs throughout the document. The ERG's focus on ICERs not only ignore NICE's instructions, but also indicates ERG's bias against ultra-orphan drugs by providing an unsolicited opinion about evaluation of highly specialized technologies. Additionally, NICE instructed both the ERG and Alexion to treat the current NICE submission separately from previous eculizumab submissions, including the submission made to the Advisory Group for National Specialised Services (AGNSS).	The ERG should remove all ICERs and discussion of ICERs from its report. The ERG also should remove references to previous eculizumab submissions including the AGNSS submission.	NICE's instructions to the ERG and Alexion were to not include ICERs and references to previous submissions.	This is not a factual inaccuracy. At the request of NICE, the ERG has removed ICERs produced using the manufacturer's model and the ERG's exploratory model. The ICERs for eculizumab versus standard care, based on the manufacturer's model to AGNSS, are available in the public domain. These represent the only existing relevant economic evidence for eculizumab in the literature / grey literature and were not discussed in the manufacturer's submission to NICE. Therefore we have mentioned them. The inclusion of ICERs in the ERG report does not reflect a bias against eculizumab or any other highly specialised technology. Rather, it reflects a view that there is a need to consider the balance between the additional health benefits generated by a technology and the health forgone as a consequence of curtailing existing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			treatments and services in order to fund that technology. The ERG also note however that at no point did the ERG report suggest whether eculizumab is cost-effective or not, nor did it suggest whether a threshold exists or what value this might take.

Issue 23 **<u>Factual inaccuracies related to the impact of the technology beyond direct health benefits: Scenario analysis</u>**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's report on page 128 states the following: "Whilst not clear from the MS, the ERG assumes that lower levels of effectiveness are intended to relate to the percentage of patients receiving eculizumab (with complete cure for each individual patient) rather than the percentage of patients in whom eculizumab is clinically effective. None of the three scenarios however reflect the levels of uptake assumed within the NHS budget impact analysis presented in Chapter 7 [redacted]."…"The estimates appear to assume that all aHUS patients will no longer lose	The ERG should clarify in its report that this scenario analysis does not relate to the percentage of patients receiving eculizumab.	The ERG appears to have misunderstood the purpose of the scenario analysis the manufacturer presented related to the impact of the technology beyond direct health benefits; a clarification is needed in the ERG's report.	This is not a factual inaccuracy. The submission was unclear and we have raised this as an issue within the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
productivity after starting treatment with eculizumab. This appears to implicitly assume that all patients will effectively be cured by the treatment." The estimate of non-direct healthcare costs was provided to help NICE appreciate the potential for economic benefits from a broader societal perspective. As the ERG is undoubtedly aware, given the rarity of aHUS and the challenges in collecting data, there is little information to directly link the benefits of eculizumab to cost savings outside of the health and social care system. Accordingly, when presenting the estimates, Alexion chose to present three scenarios concerning the extent to which the clinical benefit translated to a reduction in the societal costs associated with aHUS. These scenarios were a 100%, 75% or 25% reduction. These estimates were not supposed to represent a level of patient uptake and are unrelated to the budget impact modelling.			

Issue 24 <u>Factual inaccuracies related to the impact of the technology beyond direct health benefits: Ex-carer costs</u>

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 130: "It is	The ERG should	As the data provided in the manufacturer's	The MS does not include bibliographic

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
unclear why ex-carers should be included in any analysis of productivity losses. Their inclusion seems to assume that these individuals, if out of work, will be unemployed indefinitely. This is unlikely to be a reasonable assumption and will overestimate projected cost-savings." Data included in the manufacturer's submission provides evidence as to why ex-carers should be included in analyses of productivity loses. Specifically, on page 191 of the manufacturer's submission (Appendix G), its noted: "The household income of ex-carers is about a half of household income of general population (McLaughlin and Ritchie 1994)." McLaughlin and Ritchie's survey of ex-carers concludes "that there are long-term negative financial effects of caring, which the social security system appears to ignore." They cite previous research stating that "long-term financial losses… were experienced by almost all the carers". The survey found that the potential earning capacity after caring was greatly reduced. Specifically, "Even if they do return to some employment their job prospects will be low because of loss of skills, careers or occupational moves. Moreover, their opportunities to save money or to accrue	update its report to clarify the reason why ex-carer productivity losses were included in the manufacturer's submission.	submission notes, ex-carers face large household income loses and therefore should be included in an analysis of productivity loses.	details for McLaughlin and Ritchie. Without the opportunity to see this paper/source, it is not possible to determine its validity. We do note however that the publication is nearly 20 years old and that the survey was likely undertaken even earlier, and that no details are provided with respect to the characteristics of the study subjects included.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
pension entitlement will have been greatly reduced. It is in these financial circumstances that many long-term carers will find themselves in their fifties as they move towards pensionable age.”			