PUBLIC SUMMARY DOCUMENT

Product: ECULIZUMAB, 300 mg/30 mL injection, 1 x 30mL vial injection, Soliris®
Sponsor: Alexion Pharmaceuticals Australasia Pty Ltd
Date of PBAC Consideration: 25 August 2014

1. Purpose

1.1 To provide advice to the Minister under s101(3) of the *National Health Act 1953* (Act) in relation to its views as to the appropriateness of the initiation and continuation criteria proposed by the Department of Health (Department) on 17 July 2014 and the alternate criteria proposed by Alexion Pharmaceuticals Australasia (Alexion) on 29 July 2014, particularly as those criteria relate to the duration of the initial period of PBS subsidised treatment, and to the criteria for restarting PBS-subsidised therapy.

2. Background

2.1 At its meeting of March 2014, the PBAC recommended eculizumab on the Pharmaceutical Benefits Scheme (PBS) for the treatment of atypical Haemolytic Uraemic Syndrome (aHUS) on the basis that it should be available only through special arrangements under section 100. As outlined in the March 2014 Minutes, these arrangements include (but are not limited to):

> 6.47 The PBAC noted that the cost effectiveness of eculizumab would be significantly affected by the anticipated clinical practice of indefinite continuation of therapy. The PBAC considered that for patients who are able to demonstrate a response to the point that they achieve remission, it would be reasonable for PBS-subsidised treatment to discontinue after six months given that eculizumab is not without side effects, with clinical progress monitored and the need for further treatment assessed.
>
> 6.52 A Managed Entry Scheme would enable the listing of eculizumab at a price justified by the existing evidence, as follows:
> - the price requested in the submission for those patients with first presentation of aHUS who achieve complete remission and non-dialysis dependent patients with recurrent aHUS who achieve complete remission. The PBAC considered that complete remission would require a patient to have no TMA and to have normal renal function at six months from the initiation of therapy. In patients with recurrent aHUS, complete remission would require no TMA and renal function equivalent to their baseline at six months.
> - Scaled rebates would be applied for those patients who do not achieve complete remission at 6 months. The sponsor would be required to rebate the Commonwealth:
> - [redacted] of the price of eculizumab for patients initially requiring dialysis who achieve dialysis independence after 6 months of eculizumab therapy.
> - [redacted] of the price of eculizumab for patients who did not require dialysis and who achieve a >25% improvement in renal function where the renal function remains abnormal but is not classified as end stage renal disease.
> - the full price of eculizumab in those patients who:
>
> (i) fail to achieve a >25% improvement in renal function;
> (ii) die within 6 months; or
> (iii) have established end stage renal disease.

Process following the March 2014 recommendation

2.2 Following the March 2014 PBAC meeting, the Department negotiated with Alexion regarding the elements of the "managed entry scheme" recommended by the PBAC and the PBS restrictions, including the initiation and continuation criteria.

2.3 A set of PBS restrictions for eculizumab were proposed in a letter from the Department to Alexion on 17 July 2014. These restrictions had been developed in an iterative fashion following consultation with clinicians, patients, patient advocates and the sponsor. The consultation process included a stakeholder meeting held on 24 June 2014.

2.4 The restrictions proposed in the letter from the Department included initiation criteria, continuation criteria at 6 months ('treatment response' and 'treatment failure'), continuation criteria at 24 months, and criteria for recommencement of eculizumab after a recurrence of aHUS in patients in whom PBS-subsidised treatment is ceased after 24 months.

2.5 The background to the Department's proposal for a 24 month continuation criteria (as opposed to the 6 months recommended by PBAC in March 2104) includes that:

- Following consultations with clinicians, patients and the sponsor including at the 24 June 2014 stakeholder meeting, it was considered that a longer period than the six months recommended by the PBAC might be needed to maximise the chances of treatment success. There was some new information provided by the sponsor prior to the stakeholder meeting that provided inferential support for this position, including study results up to 24 months. As a result, the outcomes of the stakeholder meeting were an initial period of PBS-subsidised eculizumab treatment of 12 months, except in those patients with limited organ reserve who would be eligible to continue treatment beyond 12 months.

- The Department's letter of 17 July 2014 extends the 12 month period to 24 months stating that, given the sponsor's "insistence that any rebates to give effect to the 'pay for performance' framework recommended by the PBAC be conditional upon a two year period of treatment (the Department) agreed to this compromise in the interest of expediting the listing." The letter from the Department further stated that the sponsor's "demand for a minimum two years of treatment is a substantial departure from both [the 6 and 12 month continuation criteria previously proposed], and has been made despite the fact that limited clinical trial data was provided to the PBAC beyond the first year of treatment and that the vast majority of patients demonstrated an improvement within the first year of therapy."

2.6 The 24 month continuation criteria proposed in the Department's letter dated 17 July 2014, are reproduced at Figure 1.

Figure 1. Department's proposed 24 month continuation criteria

Continuation criteria at 24 months (written application FAX TO MEDICARE)

Continuing treatment

After 24 months initial treatment with eculizumab, patients are only eligible for continuing treatment if the patient demonstrates both of the following:

1. An ongoing 'treatment response' (defined as in 6 month continuation criteria);

AND

2. The patient has limited organ reserve, defined as either:
   - Severe cardiomyopathy, severe neurological impairment, severe gastrointestinal impairment, severe pulmonary impairment, related to TMA; **OR**
   - Grade 4 or 5 chronic kidney disease (eGFR <30ml/min).

2.7 Alexion, in its 29 July 2014 response to the Department stated that it

> "cannot agree to the 24 month restriction criteria as per currently proposed wording by the DoH due to the significant risk to patient safety. Unless we reach agreement on this critical point, Alexion cannot proceed further in these negotiations because your proposal stipulates that ALL patients who benefit the most will be removed from therapy and await their next crisis in the form of a reoccurrence of TMA. As we have consistently stated, due to the nature of this disease and its immediately life-threatening nature of recurring TMAs in the most high risk patients, Alexion is extremely concerned with such an unethical approach in this entire patient cohort as described in DoH restriction criteria wording at 24 months."

2.8 The alternative continuation criteria proposed by Alexion in its letter of 29 July 2014, as slightly modified by its submission of 18 August, are reproduced at Figure 2.

Figure 2. Alexion's proposed 24 month continuation criteria

24 Month Continuation Criteria for those Responding Patients at Higher Risk

Patients without evidence of an identified increased risk factor would be funded continuously only through 2 years of treatment and would be carefully monitored with protocol-driven follow-up post treatment discontinuation. If any TMA occurrence should happen, patient would be immediately re-started, and funded continuously without subsequent 24 month risk factor evaluation since patient would have already been demonstrated to have met at least one risk factor (below).

Patients with evidence of any one or more identified increased risk factor would be continuously funded from the 24 month period forward, if they additionally meet the every 6 month treatment continuation criteria and would continue to be monitored with the same every 6 month treatment continuation criteria.

The identified increased risk factors are any one of the following:
1. Patient with a history of kidney transplant
2. Patient with a history of >1 occurrence of TMA manifestation
3. History of severe, TMA-related extra-renal complication/s prior to eculizumab initiation OR Within 6 months of 24 months of ongoing treatment limited extrarenal organ reserve including: severe cardiovascular impairment, - severe neurological impairment; severe gastrointestinal impairment; or severe pulmonary impairment.
4. Family history of TMA, kidney impairment, or premature mortality with suspicion of TMA involvement.
5. Identified genetic mutation or polymorphism associated with aHUS, indicating medical evidence of permanent genetic change to patient's inflammatory state.
6. eGFR <60 ml/min or proteinuria or haematuria within 6 months of 24 months of ongoing treatment

For any patient for where there is a concern by a responsible physician requesting reconsideration of treatment initiation or continuation for a specific patient, the responsible physician may require immediate 24 hour convening of established Approved Clinical Authority by the DHS/HSDP. Approved clinical authority will provide its recommendation within 24 hours of convening (within 48 hours of initial physician request) to Department of Human Services, Highly Specialised Drugs Program, who shall be obligated to follow such recommendation.

"Approved clinical authority" refers to a committee or contracted expert recognised by the Ministry of Health, DoH and DHS under this policy as having sufficient medical expertise to assess applications for patients with exceptional circumstances where lack of treatment will place the patient at higher risk of either early mortality or significant morbidity.

(Source: pg 2-3 of letter from Alexion to Department of Health, 29 July 2014)

The PBAC noted that, with the exception of the 'continuation criteria at 24 months' the elements of the restriction were largely agreed between the Department and Alexion, as outlined on page 11 of Alexion's submission.

3. Evidence provided to PBAC for consideration

3.1 The PBAC considered the following:

- The Request for advice from Department dated 11 August 2014, which included:
  - Eculizumab Minutes from March 2014 PBAC meeting
  - Letter from Department of Health to Alexion of 17 July 2014
  - Letter from Department of Health to Alexion of 22 July 2014
  - Alexion letter to the Department of Health of 29 July 2014

- Additional information from the sponsor (provided by sponsor on 12 August):
  - Alexion Terms Sheet for Deed of Arrangements 17 July 2014
  - Alexion Terms Sheet for Deed of Arrangements 18 July 2014 clean
  - Model for PFP and CR calculations 17 July 2014

- Submission from sponsor (provided by sponsor on 18 August):
  - Alexion's PBAC extraordinary submission FINAL
  - Zip folder with references

- aHUS registry protocol
- Electronic CRF for the registry
- TGA approved prescribing information for eculizumab
- Budget impact model

- Supplementary information and revised folder of references (provided by sponsor on 21 August):
  - List of references, with new references highlighted (includes those not previously seen by the PBAC)
  - New zip folder of references (to address inconsistencies between reference folder provided and the articles referred to in the submission)
  - March 2014 Electronic agenda item for eculizumab (including submission)

- The 25 June 2014 stakeholder meeting outcome statement:
  - Draft stakeholder meeting outcome statement circulated by the Department
  - Responses received by the Department to that draft

Clinical evidence

3.2 The PBAC noted that the sponsor's submission referred to a number of new publications that had not been included in the March 2014 PBAC submission. The full list of these publications is provided in Attachment A.

3.3 The PBAC noted that several publications referred to in the August 2014 submission were initially omitted from the references supplied.

3.4 The tables below include the key studies from the March 2014 submission. They have been reproduced from the March 2014 PBAC minutes and updated to include new information provided in Alexion's August 2014 submission. New information is indicated in italics.

Publication list *with new information provided to the August 2014 out of session PBAC meeting italicised*

Trial ID	Protocol title/Publication title	Publication citation
Eculizumab studies		
C08-002	Clinical Study Report C08-002 A/B: Eculizumab (Soliris) C08-002A/B an Open-label, Multi-center Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma Therapy-Resistant Atypical Hemolytic Uremic Syndrome (aHUS) Eculizumab efficacy in AHUS pts with progressing TMA, with or without prior renal transplant." *Time To Hematologic and Renal Improvements In aHUS Patients With Progressing Thrombotic Microangiopathy Treated with Eculizumab for Two Years*[a]. *Eculizumab in Atypical Hemolytic Uremic Syndrome Patients with Progressing TMA: Continued Improvements at 2-Year Follow-Up.*	Legendre et al 2013 NEJM. 368(23), 2169-2181. *Muus P, Legendre C, Delmas Y, Herthelius M, Bedrosian CL, Loirat C. Blood, 2013; 122(21): 2186.* *Legendre C, Greenbaum L, Babu S, et al. American Society of Nephrology, Abstract SA-OR101, 2012; November 3, 2012*
C08-003	Clinical Study Report C08-003A/B: An Open-Label, Multi-Centre Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma therapy-Sensitive Atypical Hemolytic Uremic Syndrome (aHUS) Hematologic and renal improvements in atypical haemolytic uremic syndrome patients with long disease duration and chronic kidney disease in response to eculizumab. Terminal complement inhibitor eculizumab in atypical haemolytic-uremic syndrome. (C08-002 and C08-003) *Eculizumab is Effective in Atypical Hemolytic Uremic Syndrome Patients with a Long Disease Duration and Chronic Kidney Disease: 2-Year Data* *Time To Hematologic and Renal Improvements In Atypical Hemolytic Uremic Syndrome Patients With Long Disease Duration and Chronic Kidney Disease (CKD) Treated With Eculizumab.*[b]	Legendre et al 2013 NEJM. 368(23), 2169-2181. Licht et al 2013 (a) Pediatric Nephrology 28 (8): 1565-1566. Legendre et al 2012(d) N Engl J Med 368(23): 2169-2181 *Licht C, Muus P, Legendre C, et al. American Society of Nephrology, Abstract SA-OR103, 2012; November 3, 2012.* *Licht C, Muus P, Legendre C et al. Blood, 2013; 122(21): 2186.*
C10-003	Interim Clinical Study Report C10-003: An open-label, multi-center clinical trial of eculizumab in pediatric patients with Atypical Hemolytic Uremic Syndrome (aHUS)	Greenbaum et al 2013.
C10-004	Interim Clinical Study Report C10-004: An open-label, multi-center clinical trial of eculizumab in adult patients with Atypical Hemolytic Uremic Syndrome (aHUS)	Fakhouri et al 2013 (d); ASN abstract
Supportive care studies		
Noris 2010	Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype.	Noris et al 2010 Clinical Journal of The American Society of Nephrology 5:doi:10.2215/CJN.02210310
Fremeaux-Bacchi 2013	Genetics and outcome of atypical hemolytic uremic syndrome: A nationwide French series comparing children and adults.	Fremeaux-Bacchi et al 2013. Clinical Journal of the American Society of Nephrology 8(4): 554-562.

Trial ID	Protocol title/Publication title	Publication citation
Kremer Hovinga 2010	Survival and relapse in patients with thrombotic thrombocytopenic purpura.	Kremer Hovinga et al 2010. Blood 115(8): 1500-1511.
Coppo 2010	Predictive Features of Severe Acquired ADAMTS13 Deficiency in Idiopathic Thrombotic Microangiopathies: The French TMA Reference Center Experience.	Coppo et al 2010. PLoS 5, (4) e10208.

Italics = new information in the August 2014 submission

[a] *Article was incorrectly titled in the submission's reference list. Poster was supplied. Conference abstract is publicly available.*

[b] *Poster titled '*Hematologic and Renal Improvements in Response to Eculizumab in Atypical Hemolytic Uremic Syndrome Patients With Long Disease Duration and Chronic Kidney Disease*' was provided in the submission's references. The conference abstract referred to in the submission's reference list is publicly available.*

3.5 The key features of the studies considered by PBAC in March 2014, and the additional information provided in the August 2014 submission, are presented in the table below.

Trial	N	Design/ duration	Patient population	Outcome(s)	*Additional information provided*
Eculizumab studies					
C08-002	17	Prospective single arm; follow up ranged from 0.5 to 3.5 years	Adult aHUS (short duration aHUS)	- Haematologic normalisation - TMA response - CKD improvement (eGFR) - HRQoL change	*<u>2 year follow-up:</u> 15 patients completed the 26-week study and 13 continued into the extension period.* - *Muus et al Blood 2013 – mean change in platelet count, haemoglobin, haptoglobin and eGFR from baseline. Cumulative percent of patients achieving key endpoint criteria during the study period. Timing of adverse events.* - *Legrende et al, 2012 (presentation to American Society of Nephrology)*
C08-003	20		Adult & adolescent aHUS (long duration of aHUS and CKD)		*<u>2 year follow-up</u>: 20 patients completed the 26-week study and 19 continued into the extension period* - *Licht et al, Blood 2013 - mean change in eGFR from baseline. Cumulative percent of patients achieving key endpoint criteria during the study period. Timing of adverse events.* - *Licht et al 2012 (presentation to American Society of Nephrology)*
C10-003	22		Paediatric aHUS		*Not referred to in the August 2014 submission*
C10-004	41		Adult aHUS		*Not referred to in the August 2014 submission*
Supportive care studies					
Coppo 2010	51	Observational registry based studies; follow up ranged from 1 to 7.5 years	Adult TTP & aHUS	Survival, ESRD, relapse, flare-up	*Not referred to in the August 2014 submission*
Kremer Hovinga 2010[a]	201		Adult and paediatric TTP & aHUS	Death and time to relapse	*Not referred to in the August 2014 submission*
Noris 2010	260		Adult and paediatric aHUS	Remission, death, ESRD, relapse, mutations	*No new information provided*
Fremeaux- Bacchi 2013	214		Adult and paediatric aHUS	Death, ESRD, relapse, mutations	*No new information provided*
Australian TMA registry	39		Adult aHUS	Death, laboratory outcomes, kidney function	*Update provided regarding patient mortality. Update also provided regarding the Australian cohort of the aHUS Global registry.*

Source: Compiled during the evaluation

aHUS = atypical haemolytic uraemic syndrome; TMA = thrombotic microangiopathy; HRQoL = health related quality of life; CKD = chronic kidney disease; ESRD = end stage renal disease; TTP = thrombotic thrombocytopenia purpura; eGFR = estimated glomerular filtration rate.

4. PBAC consideration of the evidence

4.1 The PBAC's discussion was focused, *inter alia*, on three broad areas: the need for continuous eculizumab treatment for aHUS; the optimal duration for any initial treatment period for those patients who had not failed at 6 months; and the categories of patients in whom treatment should be continued beyond any initial period.

a. Clinical outcomes following eculizumab cessation and following re-commencement of eculizumab after a recurrence of aHUS

4.2 The sponsor's submission stated that "severe thrombotic microangiopathy complications were observed after eculizumab discontinuation in the aHUS clinical studies" (pg 10) and "These cases demonstrate broad variability in the time from eculizumab removal to clinical presentation of TMA manifestations, exemplifying the difficulty in monitoring patients post discontinuation" (pg 12). The evidence provided in the submission to support these statements included:

- the Product Information which states "In aHUS clinical studies, 18 patients (5 in the prospective studies) discontinued SOLIRIS® treatment. Seven (7) severe thrombotic microangiopathy complications were observed following the missed dose in 5 patients and SOLIRIS® was re-initiated in 4 of these 5 patients".
- Legendre et al, 2013 (report of studies C08-002 and C08-003) which states "Five of 18 patients who missed eculizumab doses in our two prospective trials or a retrospective study had severe subsequent complications of thrombotic microangiopathy." The references for this are the *United States Prescribing Information* and the *Electronic Medicines Compendium. Soliris: summary of product characteristics*.
- A reference to 'Data on File, Alexion 2014'

4.3 The PBAC could not evaluate the above information because the supporting data, although apparently held by Alexion, was not provided. For example, it was not possible for the PBAC to determine the clinical outcomes of the 18 patients referred to in the Product Information, including the number who experienced a recurrence; whether the 4 patients in whom eculizumab was re-initiated were salvaged; the duration of follow-up of these patients; and the definition of 'missed doses'.

4.4 Therefore, the PBAC considered that it could not rely on this information for decision-making purposes. However, the PBAC noted that the Product Information suggests that not all patients who discontinued eculizumab in the aHUS clinical studies experienced a recurrence.

4.5 The submission also suggested that "numerous case reports further demonstrate TMA-mediated organ failure and death in patients that do not continue eculizumab treatment with the approved dosing schedule" (page 12). Case studies of patients who discontinued eculizumab that were previously provided to PBAC and provided again in the August submission included:

- Carr and Cataland 2013 present a case study of a patient who, after 9 months of continuous therapy, elected to discontinue eculizumab. The patient presented 6 months later with a recurrence. Eculizumab was re-initiated and the patient 'achieved remission and became independent of hemodialysis three weeks after restarting therapy with eculizumab'.

- Mache et al 2009 present a case study of a patient with relapsing unclassified aHUS. The authors reported that "Eculizumab was effective in terminating the microangiopathic haemolytic process in two aHUS relapses, however after normalisation of complement activity, aHUS recurred and ultimately led to anuric end-stage renal failure." The patient received 4 doses of eculizumab (600mg per dose) over the clinical course described: the first was a single dose administered 12 weeks after the first presentation of aHUS; with the subsequent 3 doses administered following the next relapse (refer to Attachment A for further information).

- Zuber et al 2012 presents a case series of 13 renal transplant recipients who were treated with eculizumab for post-transplant recurrence of aHUS. In the case series:

    - Three patients ceased eculizumab. While all three experienced a recurrence of aHUS, the PBAC noted that two of the patients had received only a single-dose of eculizumab. The other patient received 8 months of continuous eculizumab, which was then tapered off and ceased. Three months after eculizumab was stopped, a relapse was triggered by influenza vaccination. This was described as a "mild relapse, easily controlled by eculizumab re-initiation". Eculizumab was subsequently spaced to an every other month dose regimen. At the last follow-up (14 months), the patient's creatinine level was 123mcgmol/L.

    - two patients had mild aHUS relapses (a total of three recurrences) after a 6- to 8-day delay in eculizumab maintenance dose. The relapses were rapidly responsive to eculizumab re-initiation. In one of these patients, maintenance doses were eventually spaced again to every 3 weeks, without further relapse.

b. Registry data regarding the natural history of aHUS

4.6 The August submission referenced the case series of 214 patients with aHUS who were enrolled in a French registry between 2000 and 2008 (Fremeaux-Bacchi et al 2013). This registry data was included in the March 2014 submission and provides insight into the natural history of aHUS prior to the introduction of eculizumab.

4.7 The PBAC noted that, as shown in the tables below, this case series found:

- The majority of mortality and end stage renal disease occurred in the first year after diagnosis: 56% of the adults and 29% of the children experienced end stage renal disease or death within 1 year of follow-up.
- Most patients who relapsed had their first relapse in the first year after diagnosis: (69% overall). 57% (16 of 28) and 82% (19 of 23) of the first aHUS relapses occurred during the first year of follow-up in children and adults, respectively.
- Not all patients experienced a relapse of aHUS during the follow-up period (of 68 months in children and 52 months in adults), with relapses occurring in 43% of children and 35% of adults who survived the first aHUS episode without reaching end stage renal disease. Further, among the patients who were alive and without ESRD at 1 year, 47% (25 of 53) of the children and 20% (11 of 55) of the adults experienced at least one relapse during the follow-up period.

Cumulative rate of ESRD or death according to time after aHUS onset

ESRD/death	Children (n=89)	Adults (n=125)
At 1 month	15 (17%)	57 (46%)
At 1 year	26 (29%)	70 (56%)
At 5 years	32 (36%)	80 (64%)
At last follow-up	35 (39%)	89 (71%)
Median follow-up (months)	45 (1-493)	57 (1-353)

Source: Supplementary Table 3.2. Supplemental data, Fremeaux-Bacchi et al 2013.

Relapse pattern in patients who had not reached ESRD or died at the first aHUS episode.

ESRD/death	Children (n=65)	Adults (n=66)
First relapse	28 / 65 (43%)	23 / 66 (35%)
First relapse < 1 year	16 / 65 (25%)	19 / 65 (29%)
First relapse >1 yr	12 / 65 (18%)	3 / 65 (5%)
Relapse >1 yr – patients who had not reached ESRD or died at the 1-year follow-up (including patients with the first relapse during the first year of treatment)	25 / 53 (47%)	11 / 55 (20%)
Follow-up (months)	68 (2-444)	52 (2-298)

Source: Supplementary Table 3.3. Supplemental data, Fremeaux-Bacchi et al 2013.

c. Time to haematological and renal improvements in aHUS patients treated with eculizumab for periods of up to two years

4.8 The August submission provided updated data (two years of follow-up) regarding the time to improvements for two eculizumab studies that were considered as part of the March 2014 PBAC submission: the C08-002 study conducted in patients with clinical evidence of progressing TMA; and the C08-003 study in patients with a long duration of aHUS and chronic kidney disease.

4.9 The submission (pg 12) referred to "continuous, time-dependent clinical improvements demonstrated with sustained eculizumab treatment". However, the PBAC noted that the updated data showed that most of the improvements occurred within the first six months, with some continuing improvements to 12 months. For example, rapid improvements in haematological parameters were seen in both studies, with 88% and 90% of patients achieving haematological normalisation at one year in studies C08-002 and C08-003, respectively. No further patients achieved haematological normalisation at two years.

Time to haematological and renal improvements in aHUS patients treated with eculizumab for two years

	C08-002 - Patients with clinical evidence of progressing TMA (n = 17; 15 patients completed the 26 week study, 13 continued into the extension period)			**C08-003; Patients with long duration of disease and chronic kidney disease** (n = 20; all patients completed the 26 week study, 19 continued into the extension period)		
	26 weeks	**1 year** [a]	**2 years**[b]	**26 weeks**	**1 year**	**2 years**
Proportion of patients who met the criteria for TMA event free status[c]	88%	88%[a]	88%	80%	85%	95%
Proportion of patients who met the criteria for haematologic normalisation	76%	88%[a]	88%	90%	90%	90%
eGFR change from baseline (mL/min/1.73m²)	32 (14.5-49.4)	n/a	35.2 (17.3-53.1)	6.1 (3.3-8.8)	8.0 (2.1-13.9)	7.2 (0.8-13.6)
eGFR increase of ≥15 mL/min/1.73² , n(%)	9 (53)	n/a	10 (59)	1 (5)	n/a	8 (40)

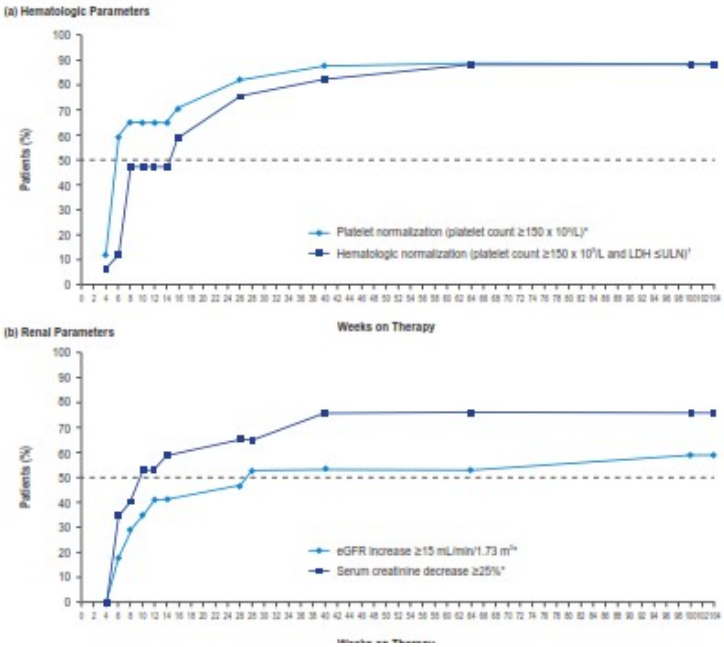
Source: Licht C, Muus P, Legendre C et al. Blood, 2013; 122(21): 2186; Legendre C, Greenbaum L, Babu S, et al. American Society of Nephrology, Abstract SA-OR101, 2012; November 3, 2012; Muus P, Legendre C, Delmas Y, Herthelius M, Bedrosian CL, Loirat C. Blood, 2013; 122(21): 2186.

[a] median duration 64 weeks (note these values are from Legrende 2012); [b] median duration 100 weeks; n/a not available

[c]Criteria for TMA event free status is: ≥12 weeks with stable platelet count, no PE/PI, and no new dialysis.

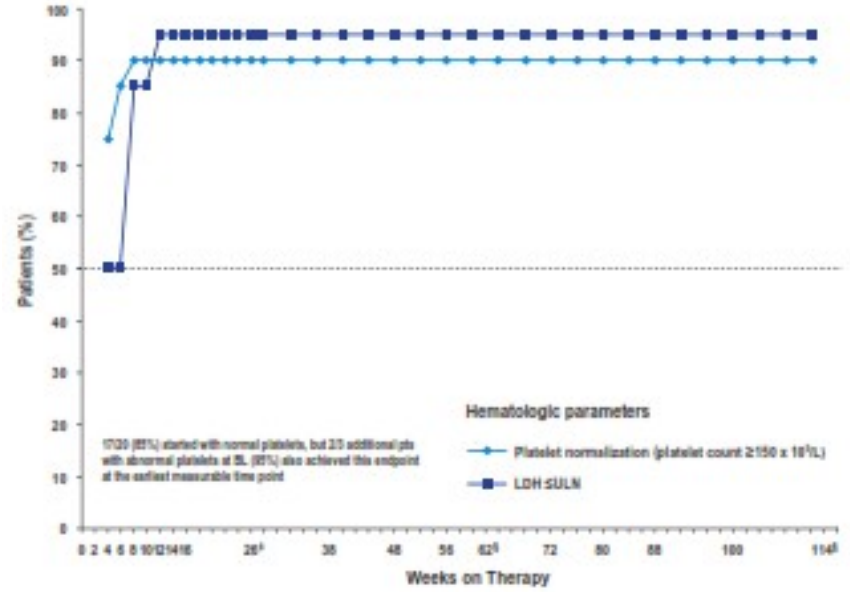
[d]Criteria for haematological normalisation is: normal platelet [≥150×10⁹/L] and lactate dehydrogenase [LDH] levels for ≥2 consecutive measurements, ≥4 weeks apart.

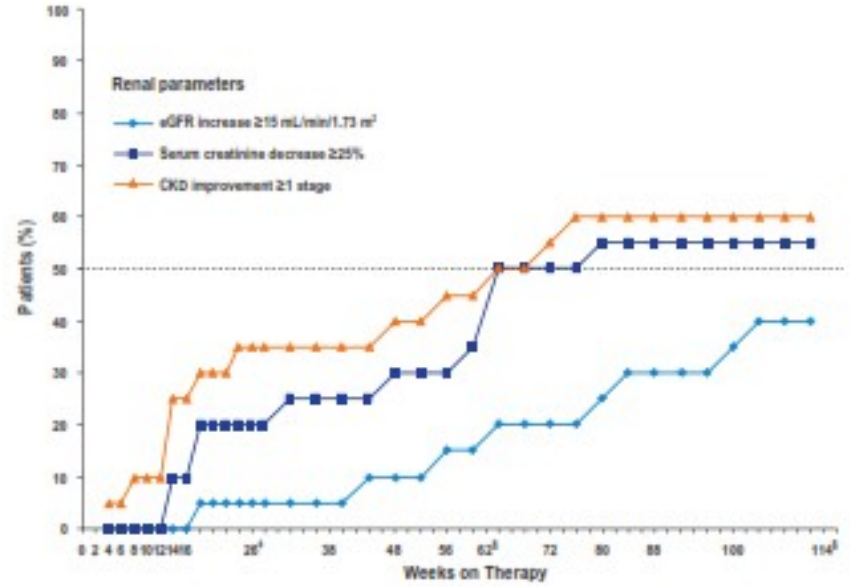
Figure 3: Cumulative percentage of patients achieving key endpoint criteria during the study period: C08-002



Muus P, Legendre C, Delmas Y, Herthelius M, Bedrosian CL, Loirat C. Blood, 2013; 122(21): 2186

Figure 4: Cumulative percentage of patients achieving key endpoint criteria during the study period: C08-003





Licht C, Muus P, Legendre C et al. Blood, 2013; 122(21):

4.10 With regard to renal function, the submission noted that in study C08-003 (patients with a long duration of disease and chronic kidney disease) the proportion of patients with an eGFR increase of >15ml/min increased from 5% at 26 weeks to 40% at two years (shown by the light blue curve in Figure 4(b) above). While noting this, the PBAC also considered other evidence about the changes in renal function over time with on-going eculizumab therapy:

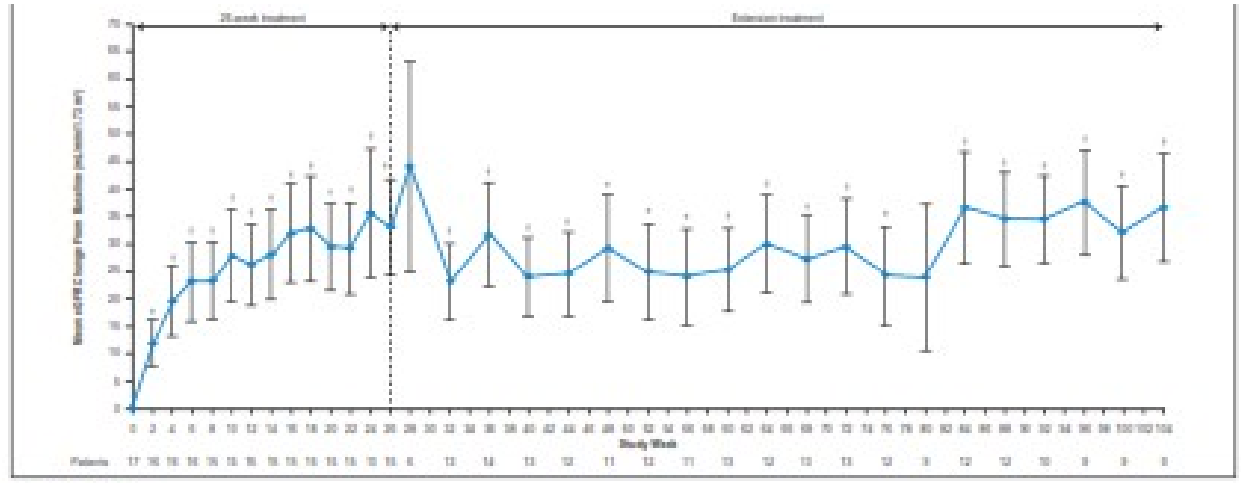
- Patients in study C08-002 (patients with a shorter duration of disease) demonstrated a rapid improvement in renal function and the proportion of

patients with an eGFR increase of >15ml/min was 53%[1] at 26 weeks, and 59% at 2 years.

- the mean change in eGFR increased to 26 weeks, then fluctuated from 26 weeks to two years, per Figures 5 and 6.

Figures 5 and 6: Mean change in eGFR through the study period

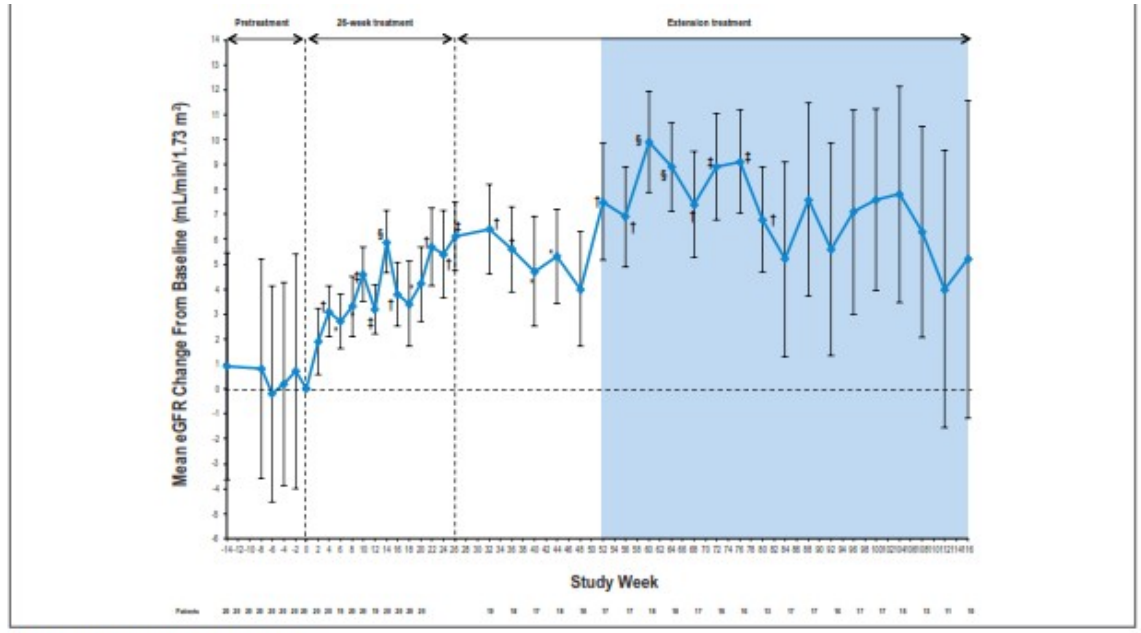
C08-002



*P≤0.05; †P≤0.01.

Muus P, Legendre C, Delmas Y, Herthelius M, Bedrosian CL, Loirat C. Blood, 2013; 122(21): 2186.

C08-003



eGFR, estimated glomerular filtration rate.
*P≤0.05; †P≤0.01; ‡P≤0.001; §P≤0.0001.

Licht C, Muus P, Legendre C et al. Blood, 2013; 122(21): 2186.

[1] Note that Legrende C et al, 2012 reports that the proportion of patients who achieve >15ml/min at 26 weeks is 53% (9 patients), rather than 47% as reported in the submission.

d. Safety of administration of eculizumab for periods of up to 3 years in aHUS

4.11 The submission stated (pg 15-16):

"The safety profile of eculizumab has been monitored globally for >10 years and during this time there have been 39 cases of meningococcal infections reported. 30 patients recovered, 3 patients recovered with sequelae and 6 patients died.

In the total eculizumab clinical trial program in aHUS (N=100), meningococcal infections occurred in 2 patients (trial C10-004; adults) over a maximum of three-years of follow-up. Both patients recovered fully and 1 remained on eculizumab therapy. "

4.12 The number of patients who experienced a serious adverse event in the two year follow-up of the C08-002 and C08-003 studies is outlined below. A serious adverse event was defined as any event that results in death, is immediately life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Number of patients who experienced a serious adverse event in study C08-002 (Patients with clinical evidence of progressing TMA)

C08-002 N=17; 15 patients completed the 26 week study, 13 continued into the extension period				
	To 6 months	**6 to 12 months**	**12 to 18 months**	**18 months plus**
Hypertension	1			
Accelerated hypertension	1	1		
Asymptomatic bacteriuria		1		

Source Legendre C et al. American Society of Nephrology, Abstract SA-OR101, 2012; November 3, 2012.

Number of patients who experienced a serious adverse event in study C08-003 (Patients with long duration of disease and chronic kidney disease)

C08-003; N=20; all patients completed the 26 week study, 19 continued into the extension period				
	To 6 months	**6 to 12 months**	**12 to 18 months**	**18 months plus**
Peritonitis	1			
Influenza			1	
Venous sclerosis at infusion site	1	1		

Source: Licht C et al. American Society of Nephrology, Abstract SA-OR103, 2012; November 3, 2012.

e. Underlying organ damage without overt signs of aHUS and mechanism of action

4.13 The PBAC noted that Alexion again argued that aHUS has a genetic basis that can be established in some patients, and that evidence of chronic complement activation in clinical remission can be detected in some patients. The August 2014 submission referred to new data from Noris et al 2014 and Cofiell et al 2013 to support the latter. Further, the submission again argued that plasma exchange/plasma infusion does not correct the underlying pathophysiology, and that without ongoing eculizumab, patients are at risk of chronic organ decline and/or catastrophic events.

4.14 The PBAC noted that complement activation in patients without overt TMA can be detected by research assays. Noris et al 2014 found that 'ex-vivo serum induced endothelial C5b-9 deposition is a sensitive tool to monitor complement activation and eculizumab effectiveness in aHUS'. The PBAC noted that the authors of this study concluded that 'C5b-9 endothelial deposits might help monitoring eculizumab effectiveness, avoid drug overexposure, and save money considering the extremely high cost of the drug'.

4.15 The PBAC recognised that assays of complement activation are largely experimental and require further investigation to determine the clinical significance of perturbations in well patients. However, the PBAC considered that this was an area where evidence is emerging and that this evolution will be likely to dictate future clinical algorithms.

f. Patient groups proposed by Alexion to be eligible for long-term eculizumab beyond the initial period

4.16 The PBAC noted that the groups of patients that the sponsor proposed to be eligible for continuous eculizumab therapy included those proposed by the Department but were substantially broader (refer to Figures 1 and 2).

- The Department's continuation criteria enable patients with limited organ reserve to receive continuing treatment, because these patients would have the least capacity to recover from a subsequent aHUS attack. This is anticipated to be a small minority of the patient cohort with aHUS.
- Alexion's proposed continuation criteria included patients with an eGFR <60mL/min (as opposed to <30mL/min proposed by the Department), a history of kidney transplant, prior history of more than one TMA manifestation, family history of TMA and identified genetic mutations.

4.17 The PBAC noted the criteria proposed by the Department took into account whether the patient is clinically able to tolerate a flare of aHUS. That is, the criteria proposed by the Department attempt to identify the groups of patients at the highest risk of morbidity and mortality if TMA-mediated end-organ damage recurred, rather than those patients at the highest risk of a recurrence.

4.18 Alexion, on the other hand, states that its criteria attempt to identify 'aHUS patients at the highest risk of morbidity and mortality if eculizumab is stopped' (pg 3 of submission). The PBAC recalled that it had already considered several of these elements as part of Alexion's proposal in March 2014, and that it had "considered that the following key pieces of information could not be determined: whether a surrogate exists for durable remission; … and whether treatment should differ by genetic sub-types or clinical scenarios" (paragraph 6.31, March 2014 PBAC Minutes). Additionally, the PBAC noted that some of the patient groups in Alexion's proposal are encompassed by the Department's criteria.

4.19 The PBAC then considered the evidence relating to each of the sponsor's six proposed risk factors in turn. The PBAC focused on:

- whether there was clear evidence of a risk of increased mortality due to a recurrence of aHUS that could reasonably be expected to be avoided by treatment with eculizumab rather than standard care.
- whether the criteria would enable the identification of patients at the highest risk of increased mortality due to a recurrence of aHUS.

1. Patient with a history of kidney transplant

4.20 The sponsor argued that patients with a history of kidney transplant have a 'very high-risk for another TMA manifestation' (pg 17). However, the PBAC noted that the submission did not provide direct evidence demonstrating that patients with a history of kidney transplant have a higher mortality rate from aHUS recurrence than those patients who do not have a history of kidney transplant.

4.21 The submission further argued that a 'renal graft has less reserve to compensate than a native kidney (Noris and Remuzzi, 2010)', and 'Once organ damage occurs, patients are more susceptible to organ failure due to the fact that there is less functioning organ to recover from the chronic complement activity insult.' However, the PBAC noted that under the criteria proposed by the Department (17 July 2014) patients with limited organ reserve would be eligible for continuing eculizumab treatment, including patients with grade 4 or 5 chronic kidney disease (eGFR <30ml/min).

4.22 Therefore the PBAC considered that those patients with a history of kidney transplant who have the highest risk of mortality following a recurrence were already covered by the Department's proposed criteria.

2. Patient history of >1 occurrence of a TMA manifestation

4.23 The submission (pg 18) asserts that patients who have a history of >1 occurrence of an overt TMA manifestation "are most obviously at continued risk for overt TMA and sudden organ failure". The PBAC considered that while the risk of relapse may be higher in these patients, no evidence was provided to demonstrate that these patients have a higher risk of mortality following a relapse.

4.24 Further, the PBAC noted that this criterion includes patients with TMA manifestations prior to eculizumab commencement, but who have not relapsed since receiving eculizumab. The natural history of aHUS in such patients is not known.

3. 'History of severe, TMA-related extra-renal complication/s prior to eculizumab initiation OR within 6 months of 24 months of ongoing treatment limited extra-renal organ reserve including
   - Severe cardiovascular impairment,
   - Severe neurological impairment
   - Severe gastrointestinal impairment; or
   - Severe pulmonary impairment.' (page 18)

4.25 The submission claimed that "Noris and Remuzzi noted that several published cases suggest that progression of extra-renal vascular lesions can occur even in the absence of TMA manifestations (Noris and Remuzzi, 2014). Removal of complement inhibition in these patients places them at high risk of imminent death due to pre-existing loss of functional reserve." (pg 18) The PBAC considered that data from Noris and Remuzzi, 2014 do not provide evidence that ongoing eculizumab reduces this risk, or that the risk is always present after successful eculizumab treatment.

4.26 The PBAC noted that under the criteria proposed by the Department (17 July 2014) patients with limited organ reserve would be eligible for continuing eculizumab treatment, including patients with severe cardiomyopathy, severe neurological

impairment, severe gastrointestinal impairment, severe pulmonary impairment, related to TMA.

4.27 However, the PBAC noted that a participant at the stakeholder meeting had commented on the meeting outcome statement in relation to the Department's proposal for patients with 'severe' cardiomyopathy related to TMA to be eligible for continuous therapy (providing other criteria are also met). The participant suggested that it may be more appropriate to include patients with 'significant cardiomyopathy' in this restriction, rather than 'severe cardiomyopathy'. The PBAC noted that left ventricular ejection fraction <40% is a widely used threshold for abnormal cardiac function. The PBAC therefore recommended that the restriction, as proposed by the Department, should be amended to replace 'severe cardiomyopathy' with 'left ventricular ejection fraction < 40%'.

4.28 The PBAC also noted that Alexion's proposed restriction allows for patients who have complications prior to eculizumab initiation or within six months of treatment, rather than after the initial treatment period. Because organ reserve may improve in the 6 to 12 month period of eculizumab therapy, the PBAC considered that it was appropriate that the limited organ reserve be observed at the end of the initial treatment period.

4. <u>"Family history of TMA, kidney impairment, or premature mortality with suspicion of TMA involvement" (page 19)</u>

4.29 The submission states that "Familial cases have worse outcomes than patients without familial history, including significantly worse progression to ESRD or death within 3 year of TMA manifestation.(Noris et al, 2010)" (page 19).

4.30 The PBAC considered that there was no clear evidence that there is a higher risk of both relapse and death after eculizumab treatment in patients with family history of TMA, kidney impairment, or premature mortality with suspicion of TMA involvement, and, in particular, whether those relapses would be associated with a higher risk of mortality.

5. <u>Identified genetic mutation or polymorphism associated with aHUS, indicating medical evidence of permanent genetic change to patient's inflammatory state.</u>

4.31 The submission stated that

"Although aHUS patients with or without an identified genetic mutation/s have a similar disease course and response to eculizumab treatment (Legendre 2013), an identified mutation or polymorphism in a gene associated with clinical manifestation of aHUS provides confirmation of the specific mechanism and aetiology of chronic uncontrolled complement activation and the inability of this specific patient to ever control complement activation in their lifetime.(Legendre et al, 2013; Noris et al, 2010; Fremeaux-Bacchi et al, 2013; Noris et al, 2014)"

4.32 The PBAC noted that the submission did not provide evidence relating identified genetic mutations to either the ability of a patient to recover from a recurrence of aHUS, and/or the optimal duration of eculizumab treatment.

4.33 The PBAC re-iterated its consideration from March 2014 that it could not determine whether treatment should differ by genetic sub-types, based on currently available information. The PBAC acknowledged that this is an area where clinical evidence is rapidly emerging and that data collection would be facilitated through the sponsor's proposed Managed Entry Scheme. The PBAC would welcome the submission of further data as it becomes available.

6. <u>eGFR <60 ml/min or proteinuria or haematuria within 6 months of 24 months of ongoing treatment</u>

4.34 The PBAC considered that proposed eGFR <60ml/min was too broad to identify those patients at highest risk of mortality following a relapse. The PBAC noted that 70% of patients enrolled in C08-002 and C08-003 had an eGFR<60mL/min at median follow-up of 64 and 62 weeks, respectively (as reported in Tables 4 and 5, Legendre et al 2012, supplementary appendix). In particular, 53% of patients in C08-002, which enrolled patients with short duration aHUS, had an eGFR<60mL/min at both 26 weeks and 64 weeks of follow-up.

4.35 The PBAC considered that a criteria to enable continuous eculizumab therapy for patients with an eGFR <30ml/min would identify those patients at the highest risk of mortality following a recurrence of aHUS.

5. PBAC advice to the Minister

5.5 The PBAC re-iterated its view from March 2014 that there is a high unmet clinical need for an effective treatment for aHUS, particularly for acute events. The PBAC reiterated there is a need to list eculizumab on the PBS to facilitate access for those patients for whom it had recommended listing in March 2014 - that is patients with active, progressive TMA during acute episodes of aHUS and who have not progressed to end stage renal disease (ESRD) i.e. greater than four months on dialysis; or for prevalent patients on chronic dialysis demonstrating extra-renal TMA.

5.6 The PBAC considered the available data continue to be of low quality, even when taking into account the difficulties of data collection in rare diseases.

5.7 However, the PBAC noted that new data regarding aHUS and its management are emerging rapidly, and encouraged the sponsor to submit new data for PBAC consideration as it becomes available, in order to enable further consideration based on more robust evidence. For example, the PBAC noted that evolving fields include: the understanding of aHUS and how treatment should be tailored based on a patient's genetic sub-type; and the role for monitoring complement activation in an approved assay that can be used in routine clinical practice.

5.8 The PBAC noted that the key arguments in the sponsor's submission regarding the need for continuous therapy included:

- "patients who discontinue eculizumab are at high risk for severe TMA complications" (pg 10). This was referenced to data held by Alexion and to the Product Information, for which supporting data were not provided; and to case studies that the PBAC did not consider to support the need for continuous eculizumab therapy in all patients. Further, registry data show that a significant proportion of patients do not experience a relapse of aHUS. For example, Fremeaux-Bacchi et al 2013 found that among aHUS patients who were alive and without end stage renal disease at 1 year, 53% of children and 80% of adults did not experience any relapses over the follow-up period of 68 months in children and 52 months in adults.

- "Re-initiation of eculizumab therapy following discontinuation cannot be relied upon to salvage organ function" (pg 10). The PBAC noted that in some cases patients achieved remission after eculizumab was re-initiated, particularly those patients who received long-term (but still less than 1 year) eculizumab treatment prior to cessation (for example, Carr and Cataland 2013 and cases 22, 10 and 20 of Zuber et al 2012).

- Patients "forego the on-going clinical improvement observed with chronic eculizumab treatment as demonstrated in the long-term follow-up studies" (pg 10). The PBAC noted that the vast majority of benefit occurs in the first 6 months of treatment, with some continuing improvement over 6 to 12 months. Further it is not known whether any on-going clinical improvement is due to the continued administration of eculizumab for two years, or represents the benefits of the drug treatment within the first 6 to 12 months.

5.9 Taking comparative efficacy into account, no convincing evidence was presented to the PBAC that demonstrated that all patients should routinely have uninterrupted, life-long eculizumab therapy. This was consistent with views recorded in the draft stakeholder meeting outcome statement that "All agreed that long-term data on the optimal dose and duration of treatment with eculizumab for patients with aHUS are lacking". In the absence of such data and considering the potential for harms with long term use, some which are already known, the PBAC re-iterated its advice from March 2014 that

> "for patients who are able to demonstrate a response to the point that they achieve remission, it would be reasonable for PBS-subsidised treatment to discontinue after [a defined period] given that eculizumab is not without side effects. Clinical progress would be monitored and the need for further treatment assessed.'

5.10 The PBAC noted the claim in the submission (page 6) that "it is highly unethical to stop treatment in the entire eculizumab-treated patient population". The PBAC considered that the converse is true, and that in standard medical practice, evidence is generally required to support the need for on-going treatment. As outlined above, the PBAC did not consider that such evidence had been supplied, nor that discontinuation of eculizumab treatment was unethical, especially if reintroduction was enabled without prejudice if the disease relapses. Given the uncertainty about the benefits of lifelong treatment, the PBAC considered that sufficient clinical equipoise existed, such that randomisation in a Human Research Ethics Committee-approved trial protocol would be an appropriate standard of care.

5.11 The PBAC noted that the rates of adverse events in the 37 patients enrolled in the C08-002 and C08-003 studies did not appear to increase over time. However, the PBAC re-iterated its view from March 2014 that

> "… the comparative safety of long-term eculizumab use is still to be determined. The safety data from the four studies of eculizumab in aHUS was for a maximum follow up of 3.5 years (with a mean follow-up of 29.4 months across all studies). The PBAC noted that eculizumab therapy may be continued lifelong in some patients, a view that was confirmed by the clinical specialist at the hearing. Further, the PBAC noted that the safety of long-term use of eculizumab in patients with complete remission of TMA and renal function in also not known." (Paragraph 6.34, ratified Minutes)

5.12 The PBAC considered that the Department's criteria provide appropriate safeguards for those patients who do relapse, noting that these safeguards include that:

- to minimise the potential for a recurrence, a patient would be required to participate in a comprehensive monitoring program after discontinuation of initial treatment with eculizumab;

- the re-initiation criteria, which enable patients who experience a recurrence of aHUS to rapidly re-commence eculizumab therapy. The PBAC further noted that the sponsor had largely agreed with the re-initiation criteria proposed in the Department's letter; and

- following re-commencement of eculizumab after a recurrence, patients would be eligible for long-term eculizumab therapy, provided they are assessed every six months for treatment response or failure, and these criteria are satisfied.

Overall, the PBAC considered that these aspects of the Department's criteria struck an appropriate balance between clinical need, patient safety and cost-effectiveness in the context of the current evidence base.

5.13 Therefore, the PBAC concluded that no evidence had been provided to cause it to alter its advice from March 2014 that for patients who are able to demonstrate a response to the point that they achieve remission, it would be reasonable for PBS-subsidised treatment to discontinue after a defined period of time (paragraph 6.47, March 2014 Minutes).

5.14 The PBAC recalled that, in March 2014, it had considered that the period of time after which it would be reasonable for PBS-subsidised treatment to be discontinued was six months. The PBAC further recalled that it had come to this conclusion in light of the rapid treatment effect observed in clinical trials, noting that eculizumab is not without side effects, and that in the context of clinical progress being monitored, the need for further treatment should be assessed.

5.15 The PBAC also noted the reasons for which a 12 month duration of initial therapy had been discussed at the stakeholder meeting, and for which a 24 month duration of initial therapy had been proposed in the Department's letter of 17 July 2014, as outlined in 'Background'.

5.16 The PBAC noted that there is no strong clinical rationale to support a particular time-frame for the initial period of eculizumab. However, the PBAC considered that the following information was relevant:

- The vast majority of the benefit occurs in the first 6 months of eculizumab treatment, with some continuing improvement in the 6 to 12 month period (based on the 2 year follow-up data of C08-002 and C08-003).

- the two year follow-up data from C08-002 and C08-003 shows that there is no consistent improvement across all parameters in the 12 to 24 month period, and it is not known whether any on-going clinical improvement is due to the continued administration of eculizumab for two years, or represents the benefits of the drug within the first 6 to 12 months. For example, improvement could reflect the time elapsed since exposure to the trigger and resolution of the active TMA.

- registry data shows that the risk of relapse is highest in the first 12 months following aHUS onset (refer to Fremeaux-Bacchi et al 2013).

5.17 The PBAC further noted that it was difficult to determine the additional value that 24 months of continuous therapy would provide compared to 12 months and that, in light of the high unit cost of eculizumab, routine use of 24 months of initial therapy would significantly increase the costs to the Commonwealth compared to 12 months.

5.18 The PBAC concluded that, in light of the evidence currently available, the most appropriate duration for initial, continuous administration of eculizumab is 12 months. The PBAC considered that this was another area in which evidence is likely to emerge rapidly, and it would welcome the provision of such data for the Committee's consideration as it becomes available.

5.19 For the reasons provided in Section 4 above, the PBAC considered that the most appropriate continuation criteria, to enable long-term administration of PBS-subsidised eculizumab should be:

Figure 7 : PBAC advice to the Minister

Continuation criteria at ~~24~~ 12 months (written application FAX TO MEDICARE)
Continuing treatment
After ~~24~~ 12 months initial treatment with eculizumab, patients are only eligible for continuing treatment if the patient demonstrates both of the following:

1. An ongoing 'treatment response' (defined as in 6 month continuation criteria);

AND

2. The patient has limited organ reserve, defined as either:
   i. ~~Severe cardiomyopathy,~~ cardiomyopathy as evidenced by left ventricular ejection fraction < 40%, severe neurological impairment, severe gastrointestinal impairment, severe pulmonary impairment, related to TMA;
   OR
   ii. Grade 4 or 5 chronic kidney disease (eGFR <30ml/min).

Changes compared to the Department's proposed 24 month continuation criteria (from Figure 1) are in strikethrough (deletions) and underlined (additions).

5.20 The PBAC noted that the sponsor had proposed that an approved clinical authority be established to

"assess applications for patients with exceptional circumstances where lack of treatment will place the patient at higher risk of either early mortality or significant morbidity."

The PBAC noted that the Department of Human Services has long-standing experience administering complex restrictions for PBS drugs through the Complex Authority Required program. The PBAC considered that this would be an appropriate

avenue for the administration of the restriction for eculizumab in the treatment of aHUS.

6 Sponsor Comments

Alexion do not agree with the PBAC criteria that ignore the rapid and irrecoverable end-organ damage or sudden death in those patients at the highest risk of severe TMA complications of aHUS. The PBAC recommendation for 12-month discontinuation criteria is in direct conflict with detailed and independent review by global regulatory authorities such as EMA, FDA, TGA, and medical experts (Legendre et al NEJM 2013), all of which accepted the principle that patients continue to incur organ damage and progressive mortality when not treated with chronic eculizumab therapy. All regulatory authorities have accepted clinical trial data that long term eculizumab treatment leads to inhibition of complement mediated TMA and markedly significant time-dependent improvements in renal function in aHUS patients. Importantly, there is no peer-reviewed data to support the PBAC's recommendation for the short-term use of eculizumab for aHUS to achieve equivalent long-term benefits seen with continuous eculizumab use. However, in the interests of patients requiring urgent access to Soliris today, Alexion are pleased that a listing date for December 1st 2014 is announced and the Government will proceed unilaterally with a PBS Section 100 listing without managed entry scheme or rebates proposed in the March 2014 PBAC meeting.

Summary of evidence

References	Population	Results
New trials provided as part of the sponsor's submission (i.e. trials that were not provided as part of the March 2014 submission)		
Boudville N, Kemp A, Moody H et al. Factors associated with chronic kidney disease progression in Australian nephrology practices. Nephron Clinical Practice, 2012; 121(1-2): c36-c41.	Retrospective study of the electronic medical records of 1,328 patients referred to Australian nephrologists. Measured change in eGFR to identify factors associated with chronic kidney disease progression	Results (from article): Univariate analysis demonstrated that women, smokers, and patients prescribed erythropoiesis-stimulating agents (ESA) had a significantly more rapid decline in eGFR (p = 0.007, 0.033, and 0.003, respectively). On multivariate analysis: gender, age, prescription of ESA and phosphate binders, and baseline eGFR were significantly associated with CKD progression.
Cofiell R, Kukreja A, Bedard K et al. Biomarkers of Complement and Endothelial Activation, Inflammation, Thrombosis and Renal Injury In Patients (pts) with aHUS Treated with Eculizumab (ECU). Blood, 2013; 122(21): 2184. *Note this was accessed at: https://ash.confex.com/ash/2013/webprogram/Paper63810.html* *Because tables and graphs were not supplied with the reference submitted by the sponsor.*	Healthy controls and adult aHUS patients from a phase 2 aHUS clinical trial. N=29-39. Biomarkers were evaluated at baseline and during 26 weeks of Ecu treatment in a Phase 2 aHUS clinical trial.	Results (from article): "All biomarkers were elevated at baseline in the majority of pts, including pts with normal platelet counts, LDH, and/or haptoglobin levels. Following Ecu treatment in all pts, coagulation markers (F1+2 and D-dimer) were significantly reduced by 2.5 wks and decreased by >50% by wk 26. Renal injury markers (U-cystatin C and U-TIMP-1) also reduced significantly by 2.5wks. Interestingly, mean plasma levels of complement Ba, a key marker of CAP activation, were significantly decreased by 4-6 wks following Ecu but remained elevated. Soluble tumor necrosis factor receptor 1 (sTNFR1) and U-clusterin levels decreased by 4-6 wks, while thrombomodulin, VCAM-1, CXCL10, U-FABP-1, U-β2m and IL-6 levels reduced more slowly (12-26 wks). By 26 wks of Ecu, levels of all renal injury markers had normalized (≈78%-90% reduction) but markers of CAP and endothelial activation, inflammation, and coagulation remained elevated relative to levels in healthy subjects." Discussion (from article) "Ecu reduced but did not normalise plasma BA (a key marker of CAP activation) suggesting ongoing complement activation (CAP), upstream of C5, and the need for sustained complement inhibition downstream. Ecu treatment rapidly and markedly reduced biomarkers of thrombin generation, fibrinolysis, and inflammation, and normalized markers of renal injury; this reduction was sustained with ongoing Ecu treatment. Endothelial activation biomarkers reduced more slowly, suggesting ongoing effects of CAP C3 activation upstream of C5. These data point to the chronicity of the disease process and support the continuous administration of Ecu in aHUS pts, including those with normal hematological markers of TMA."
Gansevoort RT, Matsushita K, van der Velde M et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int, 2011; 80(1): 93-104.	Meta-analysis of nine general population cohorts of 845,125 patients, and an additional 8 cohorts with 173,892 patients at high risk of CKD.	Results (from article): For patients in this study, 'lower eGFR and higher albuminuria are risk factors for ESRD, acute kidney injury and progressive CKD in both general and high-risk populations, independent of each other and of cardiovascular risk factors'.
Legendre C, Greenbaum L, Babu S, et al. Eculizumab (ECU) in Atypical Hemolytic Uremic Syndrome (aHUS) Patients (pts)	C08-002 (adult and adolescents with short-duration aHUS (plasma therapy resistant)	Refer to Section 4 of the Minutes.

References	Population	Results
with Progressing TMA: Continued Improvements at 2-Year Follow-Up. American Society of Nephrology, Abstract SA-OR101, 2012; November 3, 2012.	Across C08-002 and C08-003 (both 26-week studies); 32 of 37 patients continued eculizumab in the extension studies	
Licht C, Muus P, Legendre C et al. Time To Hematologic and Renal Improvements In Atypical Hemolytic Uremic Syndrome Patients With Long Disease Duration and Chronic Kidney Disease (CKD) Treated With Eculizumab. Blood, 2013; 122(21): 2186. **Note that the conference poster was supplied, while the conference abstract was the reference referred to on the reference list**	Conference abstract 2-year follow-up of **C08-003:** 20 patients completed the 26-week study and 19 continued into the extension. Adult and adolescent patients, with **a long duration of aHUS** and chronic renal impairment (plasma therapy insensitive) .	Refer to Section 4 of the Minutes
Loirat C, Noris M, Fremeaux-Bacchi V. Complement and the atypical hemolytic uremic syndrome in children. Pediatr Nephrol, 2008; 23(11): 1957-1972.	Literature review. Includes registries such as Caprioli et al 2006, Sellier-Leclerc 2007, Neumann et al 2003. Reports natural history of aHUS by genetic sub-type (eg. age at onset, triggering events, prognosis, treatments, post-transplant recurrence. Focuses on children	Results of article: The risk of post-transplant recurrence is approximately 80% in CFH or IF-mutated patients, 20% in MCP-mutated patients, and 30% in patients with no mutation. Reports that 'in the French paediatric series, of the 24 renal transplantations performed in 15 aHUS children, 16 (67%) failed. Of the 16 graft failures, eight (50%) were due to graft thrombosis and five (31%) to recurrence of HUS" (referring to Sellier Leclerc et al 2007).
Muus P, Legendre C, Delmas Y, Herthelius M, Bedrosian CL, Loirat C. Time To Hematologic and Renal Improvements In Atypical Hemolytic Uremic Syndrome Patients With Long Disease Duration and Chronic Kidney Disease (CKD) Treated With Eculizumab. Blood, 2013; 122(21): 2186.	Conference abstract 2-year follow-up of **C08-002:** 17 patients enrolled; 15 completed the 26-week study and 13 continued into the extension. Adult and adolescent patients, with **a short duration of aHUS** (plasma therapy resistant)	Refer to Section 4 of the Minutes
Noris M, Galbusera M, Gastoldi S et al. Dynamics of complement activation in atypical HUS and how to monitor eculizumab therapy. Blood, 2014.	44 patients with aHUS - 36 from the International Registry of HUS/TTP (with mutations in CFH, CFI, C3 and CFB or anti-CFH antibodies or without mutations in known genes) plus 8 aHUS patients who were treated with eculizumab; and 7 healthy relatives carrying complement gene mutations; and 7 healthy relatives without mutations/antiCFH antibodies); and 15 patients with C3G or IC-MPGN.	Aim: Study aims were to: 1) test new sensitive assays of complement activation at endothelial cell level in aHUS patients; 2) clarify whether unaffected relatives carrying complement gene mutations show impaired complement regulation on endothelium; 3) search a tool for monitoring and/or titrating anti-C5 treatment in clinical practice, taking into account that complement activation occurs on endothelium and not in fluid phase.

References	Population	Results
	Controls were 30 healthy subjects age and sex matched with patients.	Results/Discussion: By specific ex-vivo assays, we demonstrate that aHUS patients with or without identified complement gene mutations or anti-CFH antibodies, consistently and chronically activate complement on endothelium. Also unaffected gene mutation carriers show dysregulated complement activation at endothelial level. Finally, we document that the level of C5 blockade on endothelium found in our ex-vivo test predicts clinical effectiveness of eculizumab in-vivo and could guide drug dosing and timing.
Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. Nature Reviews Nephrology, 2014; 10(3): 174-180.	'Perspectives' article (literature review/editorial)	References the reported incidence of cardiovascular events in aHUS (3-10%) to Noris et al 2010 and Sellier-Leclerc 2007. Describes case reports of small peripheral artery thrombosis in children with very severe forms of aHUS. Also describes case reports of large artery stenosis – describes cases of vascular lesions in patients with ESRD or in whom renal tissue was removed (esp in children on long-term hemodialysis). Describes the case of a child who presented with aHUS at 17 months of age, underwent a kidney transplant , developed aHUS recurrence in the graft. At 10 years of age and after 7 years of chronic haemodialysis the pt developed a TIA but without the haematological symptoms of aHUS. The study's authors argued that advanced occlusion and stenosis in the carotid arteries were caused by ongoing complement-induced vascular injury and treatment with eculizumab was initiated despite no evidence of aHUS activity. Eculizumab treatment blocked progression of vascular injury and the patient underwent a successful second kidney transplant. During 18 months follow-up monitoring, no recurrence of aHUS occurred and vascular stenosis did not progress.
Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol, 2007; 18(8): 2392-2400.	46 children with aHUS. Impact of complement mutations on prognosis	A total of 52% of patients had mutations in one or two of known susceptibility factors (22, 13, and 15% of patients with CFH, IF,orMCP mutations, respectively; 2% with CFH_IF mutations). Age _3 mo at onset seems to be characteristic of CFH and IF mutation–associated aHUS. The most severe prognosis was in the CFH mutation group, 60% of whom reached ESRD or died within _1 yr. Only 30% of CFH mutations were localized in SCR20. MCP mutation–associated HUS has a relapsing course, but none of the children reached ESRD at 1 yr. Half of patients with IF mutation had a rapid evolution to ESRD, and half recovered. Plasmatherapy seemed to have a beneficial effect in one third of patients from all groups except for the MCP mutation group. Only eight (33%) of 24 kidney transplantations that were performed in 15 patients were successful. Graft failures were due to early graft thrombosis (50%) or HUS recurrence. In conclusion, outcome of HUS in patients with CFH mutation is catastrophic, and posttransplantation outcome is poor in all groups except for the MCP mutation group.
Sud M, Tangri N, Levin A, Pintilie M, Levey AS, Naimark DM. CKD Stage at Nephrology Referral and Factors Influencing the Risks of ESRD and Death. American Journal of Kidney Diseases, 2014; 63(6): 928-936.	Retrospective cohort study of 3,273 patients with CKD stages 3-5 who were referred to a nephrology clinic in Toronto prior to Dec 31, 2008.	Measured rates of progression to ESRD and death prior to ESRD. Identified risk factors associated with a higher risk of ESRD or death prior to ESRD.
Szer J, Muus P, Roeth A et al. Long-Term Safety of Sustained Eculizumab Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria. Blood (ASH Annual Meeting Abstracts), 2012; 120(21): 1260.	Patients (n = 192) receiving continuous eculizumab treatment (mean duration: 30.3 months) who were enrolled in the eculizumab PNH clinical development trials and associated extension studies were assessed for the incidence of adverse events (AEs). The incidence of AEs, irrespective of	Per article: Significantly fewer patients reported an AE in the last 26 weeks (n=145) compared with the first 26 weeks (n=189) of treatment (P<0.001); this included the most commonly reported AEs such as headache (P<0.001), nasopharyngitis (P=0.029), back pain (P=0.031), nausea (P=0.029), and fatigue (P=0.029). NH patients receiving long- term eculizumab treatment (up to 5.5 years) did not experience signs of cumulative toxicity. In fact, patients showed a significantly decreased incidence of AEs with continuous

References	Population	Results
	relation to treatment, reported during the first 26 weeks of eculizumab treatment was compared with the last 26 weeks of treatment. In patients with treatment duration <52 weeks, the incidence of AEs reported during the first 26 weeks of treatment was compared with the incidence of AEs from 26 weeks + 1 day until the patient's last dose of eculizumab	eculizumab treatment, suggesting a favorable risk- to- benefit ratio over the long term. The low discontinuation rate due to an AE suggests long- term treatment with eculizumab is well tolerated. All patients are required to be vaccinated against Neisseria meningit idis because suppression of terminal complement activity by eculizumab increases the risk of meningococcal infections. Patients were vaccinated at least 2 weeks before the first dose of eculizumab and were educated on the early signs and symptoms of these infections. Two cases of meningococcal sepsis were reported with a time to onset of 353 and 416 days. Both patients developed a strain of meningococcal infection that was not covered by their vaccination. The infections were successfully treated: 1 patient received ceftriaxone and ciprofloxacin, and the other imipenem, rocephin, vancomycin, ceftriaxone and penicillin. Both infections resolved without sequelae: 1 patient remained in the extension study and continued to receive eculizumab; the second patient withdrew from the study.
Other key references that were included in the sponsor's submission (and also the March 2014 submission)		
Carr R, Cataland S. Relapse of aHUS after discontinuation of therapy with eculizumab in a patient with aHUS and factor H mutation. Ann Hematol, 2012; 1-2.	Case study of an adult patient with aHUS and a mutation of factor H. First presentation of aHUS occurred 7 days post Cesarean section.	Patient's platelet count and LDH normalized 2 weeks after her first eculizumab dose, and she became independent of hemodialysis after 6 weeks. The serum creatinine returned to normal 12 weeks after the initiation of eculizumab. After 9 months of continuous therapy, the patient elected to discontinue therapy with eculizumab. The patient presented again 6 months later with a recurrence. Eculizumab was restarted and the patient 'achieved remission and became independent of hemodialysis 3 weeks after restarting therapy with eculizumab'
Fremeaux-Bacchi V, Fakhouri F, Garnier A et al. Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nationwide French Series Comparing Children and Adults. Clinical Journal of the American Society of Nephrology, 2013.	214 patients with aHUS who received care in France. Pts were enrolled between 200 and 2008. All patients were screened for mutations. The study protocol specifically describes diagnosis of aHUS.	Refer to main body of Minutes.
Mache CJ, cham-Roschitz B, Fremeaux-Bacchi V et al. Complement Inhibitor Eculizumab in Atypical Hemolytic Uremic Syndrome. Clin J Am Soc Nephrol, 2009; 4(8): 1312-1316.	Case Report Adolescent (17.8 years of age) with relapsing unclassified aHUS. .	Results After week 12 a single dose of eculizumab (600 mg) was administered, resulting in normalization of platelet counts within 3 d and haptoglobin levels within 5d.Subsequently, renal function improved again (PCr 5.2 mg/dl). Approximately 2 wk after recovery of complement haemolytic activity (CH50), aHUS relapsed and PCr increased to 12.5 mg/dl. Repetitive doses of eculizumab (3* 600 mg within 6 d) again led to a normalization of haptoglobin levels within 6 d. Only minor renal recovery (PCr 9.2 mg/dl) ensued and severe hypervolemic hypertension required hemodialysis again. The platelet counts (normalization within 5 d) increased only moderately, probably related to superimposed hypertensive nephropathy. In view of end-stage renal failure, eculizumab was discontinued. A subsequent aHUS relapse led to anuria. Conclusions (from abstract) "In this patient, complement inhibition by eculizumab temporarily terminated the microangiopathic hemolytic activity. Nevertheless, renal damage as a result of preceding and subsequent aHUS activity resulted in end-stage renal failure; therefore, therapeutic success may depend on early administration of eculizumab. The

References	Population	Results
		optimal duration of treatment may be variable and remains to be determined."
Zuber J, Le Quintrec M, Krid S et al. Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation. American Journal of Transplantation, 2012; no. 12: 3337–3354.	Case series of 22 renal transplant recipients: iii. 9 received prophylactic eculizumab to attempt to prevent post-transplant recurrence iv. 13 received eculizumab for post-transplant aHUS recurrence	Patients who received eculizumab for post-transplant aHUS recurrence: Eculizumab cessation - Case number 12 (also reported by Nurnberger et al 2009) describes an adult patient with post-transplant aHUS recurrence, in whom a single 600mg dose of eculizumab induced long-term remission. The patient relapsed at 21 months, and the patient returned to hemodialysis. - Case number 13 (also reported by Larrea 2010) was given a single 600mg dose of eculizumab and relapsed at 11 months, eculizumab was resumed but graft dysfunction persisted. The patient progressed towards ESRD after cessation of eculizumab (due to a severe pulmonary infection) 4 months later. - Case number 22 describes a 43 year old patient who received 8 months of continuous eculizumab, which was then tapered off and stopped. Influenza vaccination triggered a relapse 3 months after eculizumab had been stopped. Eculizumab was resumed (described on page 10 of Zuber as a "mild relapse, was easily controlled by eculizumab reinitiation") and subsequently spaced to an every other month dose regimen. The last follow-up creatinine level was 123mcgmol/L (at 14 months). Delayed doses - Case 10 describes a 42 year old (at onset of recurrence) whose maintenance dose interval has been increased to 3 weeks for the last 6 months. Two relapses have occurred after eculizumab doses had been delayed from 6 to 8 days. - Case 16 describes a 6-year old who started at 600mg/week and then 600mg every 3 weeks. - Case 20 describes a 42 year old, who had a delay of 7 days in the fifth infusion of eculizumab, and this led to a mild relapse (rise in serum creatinine and LDH levels). The patient subsequently recovered baseline renal function following re-initiation of eculizumab.