NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Contents:
The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Alexion Pharma UK

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. aHUS alliance Global Action
   b. Kidney Research UK
   c. British Association for Paediatric Nephrology
   d. UK Renal Pharmacy Group
   e. NHS England and Improvement

4. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Alexion Pharma UK

7. **Technical engagement responses from experts:**

   a. Christopher James Reardon, patient expert, nominated by aHUS alliance Global Action
   b. Prof. David Kavanagh, clinical expert, nominated by Alexion Pharma UK, National Renal Complement Therapeutics Centre, Royal College of Physicians
   c. Dr Edwin Wong, clinical expert, nominated by National Renal Complement Therapeutics Centre

8. **Technical engagement response from consultees and commentators:**
   a. aHUS alliance Global Action
   b. British Association for Paediatric Nephrology
   c. Renal Association
   d. UK Renal Pharmacy Group

9. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre

for Health Economics, University of York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating atypical haemolytic uremic syndrome (aHUS) [ID1530]

Document B

Company evidence submission

October 2020

File name	Version	Contains confidential information	Date
ID1530 ALEXION STA Document B AICCIC	**V1**	**Yes**	**5 October 2020**

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This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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In this template any information that should be provided in an appendix is listed in a box.

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Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorization for this indication, as summarized in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People who weigh 10 kg or more with atypical haemolytic uremic syndrome (aHUS) and: • who have not had complement-inhibitor treatment, or • who have had eculizumab for at least 3 months and whose disease has responded to eculizumab.	People with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) and: • who are complement inhibitor treatment-naïve, or • have received eculizumab for at least 3 months and have evidence of response to eculizumab.	Not applicable but it should be noted that wording has been aligned to the marketing authorization.
Intervention	Ravulizumab	Ravulizumab	Not applicable
Comparator(s)	Eculizumab	Eculizumab	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clinical outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clinical outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment	Not applicable but it should be noted that: • Overall survival was not a pre-specified endpoint in the ravulizumab trial programme, although deaths were captured as a safety outcome. Overall survival has been modelled in the pharmacoeconomic analyses using Office of National Statistics data and mortality data from the literature. • Disease recurrence was not a pre-specified endpoint in the ravulizumab trial programme, but TMA parameters were collected both in patients who discontinued treatment but remained on study and those who demonstrated complete TMA response and continued treatment. However, no data on recurrence are available yet, given the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life	• Health-related quality of life	limited follow up to date. Disease recurrence has been modelled in the pharmacoeconomic analyses using longer-term data from eculizumab trials and aHUS registry data. • Non-renal clinical outcomes assessed in the ravulizumab trial programme include haematological parameters (platelets, LDH, Hb). Major non-renal clinical outcomes such as thrombosis or cardiac events were captured as safety events. • Eligibility for/success of transplantation was not a pre-specified endpoint in the ravulizumab trial programme. CKD stage data (evaluated by eGFR at select target days) were captured and are used to inform transplant considerations in the economic modelling.
Key: aHUS, atypical haemolytic uraemic syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; LDH, lactate dehydrogenase; NRCTC, National Renal Complement Therapeutics Centre; TMA, thrombotic microangiopathy.			

B.1.2. Description of the technology being appraised

Ravulizumab is a monoclonal antibody (mAB) therapy that acts as a complement inhibitor, binding to the complement protein C5 within the terminal complement pathway. As a terminal complement inhibitor, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation and subsequent cell lysis, while preserving the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

Ravulizumab was designed by re-engineering eculizumab, the current standard of care in aHUS, to approximately quadruple the half-life of the drug. The extended half-life supports a longer dosing interval of 8 weeks for ravulizumab, compared with 2 weeks for eculizumab (or 4 weeks versus 2 weeks for paedeatric patients < 20 kg).

Figure 1 summarizes the mechanism of antibody recycling that confers the longer half-life for ravulizumab compared with eculizumab. The complement pathway that helps contextualize the ravulizumab mechanism of action is presented in Section B.1.3.1 (Figure 2). Table 2 summarizes the technology being appraised.

The summary of product characteristics (SmPC) and the European public assessment report (EPAR) are provided in Appendix C.

Figure 1: Mechanism of action of ravulizumab compared with eculizumab

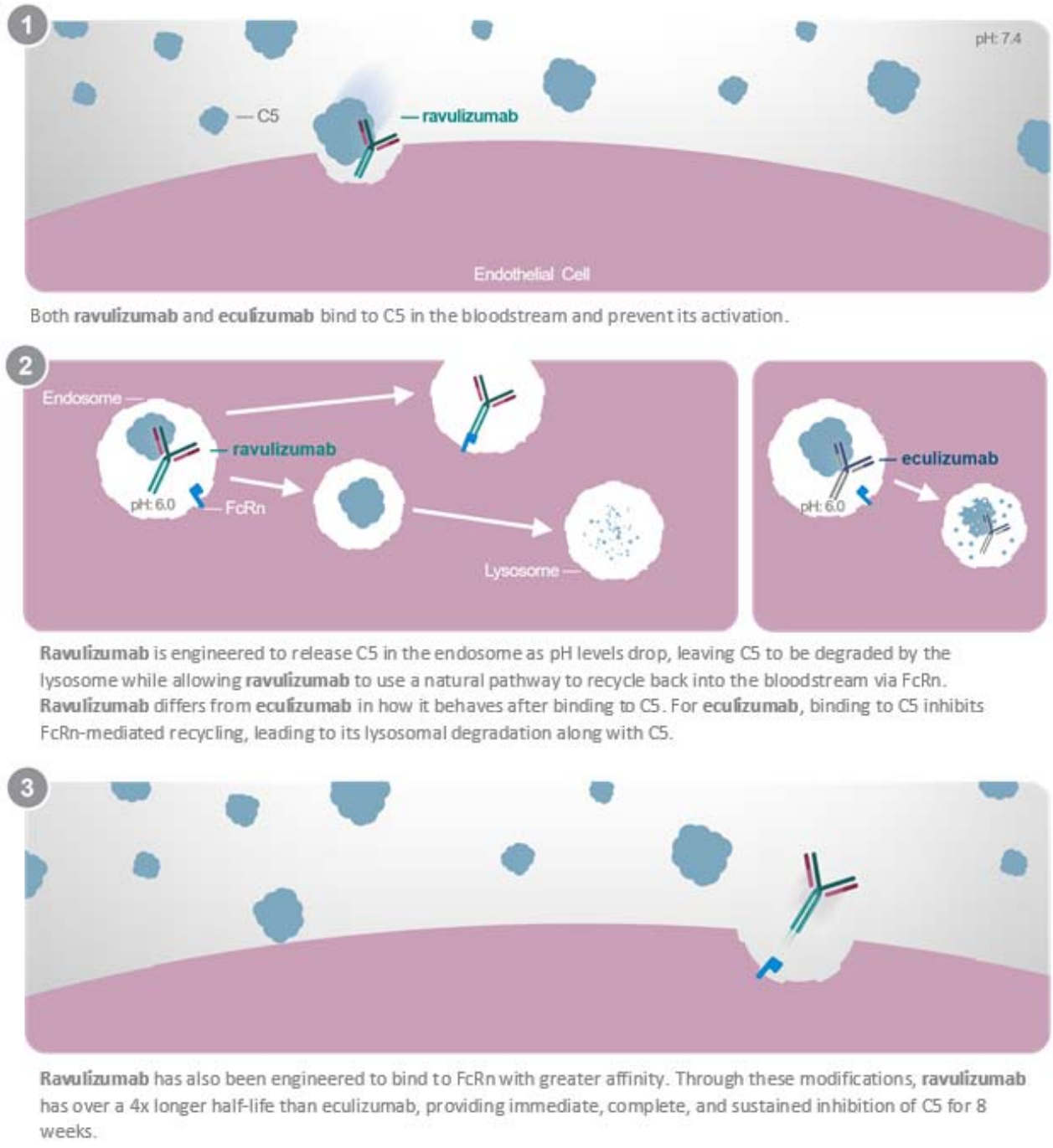


Table 2: Ravulizumab in aHUS Product Characteristics

<table>
<tr><td>UK approved name
Brand name</td><td>Ravulizumab
Ultomiris®</td></tr>
<tr><td>Mechanism of action</td><td>Ravulizumab is a monoclonal antibody IgG2/4K that specifically binds to the complement protein C5, preventing cleavage of C5 to C5a and C5b and subsequent generation of the terminal complement complex C5b-9.</td></tr>
<tr><td>Marketing authorization status</td><td>Positive CHMP opinion for the aHUS indication was received on 30 April 2020 with European Commission marketing authorization granted on 25 June 2020.</td></tr>
<tr><td>Indications and any restriction(s) as described in the SmPC</td><td>‘Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.’</td></tr>
<tr><td>Method of administration and dosage</td><td>Ravulizumab is administered by intravenous infusion.
Dosage is determined by weight as detailed below.
Dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting 2 weeks after the loading dose.
Adult patients (and paediatric patients ≥ 40 kg):
<table>
<tr><th>Body weight (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th><th>Maintenance dosing interval</th></tr>
<tr><td>≥ 40 to < 60</td><td>2,400</td><td>3,000</td><td>Every 8 weeks</td></tr>
<tr><td>≥ 60 to < 100</td><td>2,700</td><td>3,300</td><td>Every 8 weeks</td></tr>
<tr><td>≥ 100</td><td>3,000</td><td>3,600</td><td>Every 8 weeks</td></tr>
</table>
Paediatric patients:
<table>
<tr><th>Body weight (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th><th>Maintenance dosing interval</th></tr>
<tr><td>≥ 10 to < 20</td><td>600</td><td>600</td><td>Every 4 weeks</td></tr>
<tr><td>≥ 20 to < 30</td><td>900</td><td>2,100</td><td>Every 8 weeks</td></tr>
<tr><td>≥ 30 to < 40</td><td>1200</td><td>2,700</td><td>Every 8 weeks</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>None.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>List price:
£4,533 for 30 mL vial (10 mg/mL)
Regulatory review of two new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab is also ongoing with CHMP positive opinion received on 21 September 2020 and marketing authorization expected to extend to these vial sizes by November (2020).[redacted]
• £4,533 for 3 mL vial (100 mg/mL)
• [redacted] for 11 mL vial (100 mg/mL)
• Cost per mg:[redacted]
Average cost of treatment per month: £27,678*</td></tr>
</table>

Patient access scheme	A simple PAS is offered to the NHS. [redacted] PAS price: • [redacted] for 30 mL vial (10 mg/mL) • [redacted] for 3 mL vial (100 mg/mL) • [redacted] for 11 mL vial (100 mg/mL) • Cost per mg: [redacted] Average cost of treatment per month: [redacted]
Key: aHUS, atypical haemolytic uremic syndrome; CHMP, Committee for Medicinal Products for Human Use; NHS, National Health Service; PAS, patient access scheme; SmPC, Summary of Product Characteristics. **Note:** *Average monthly cost for patients on treatment over 5 years. **Source:** Ultomiris SmPC[1]	

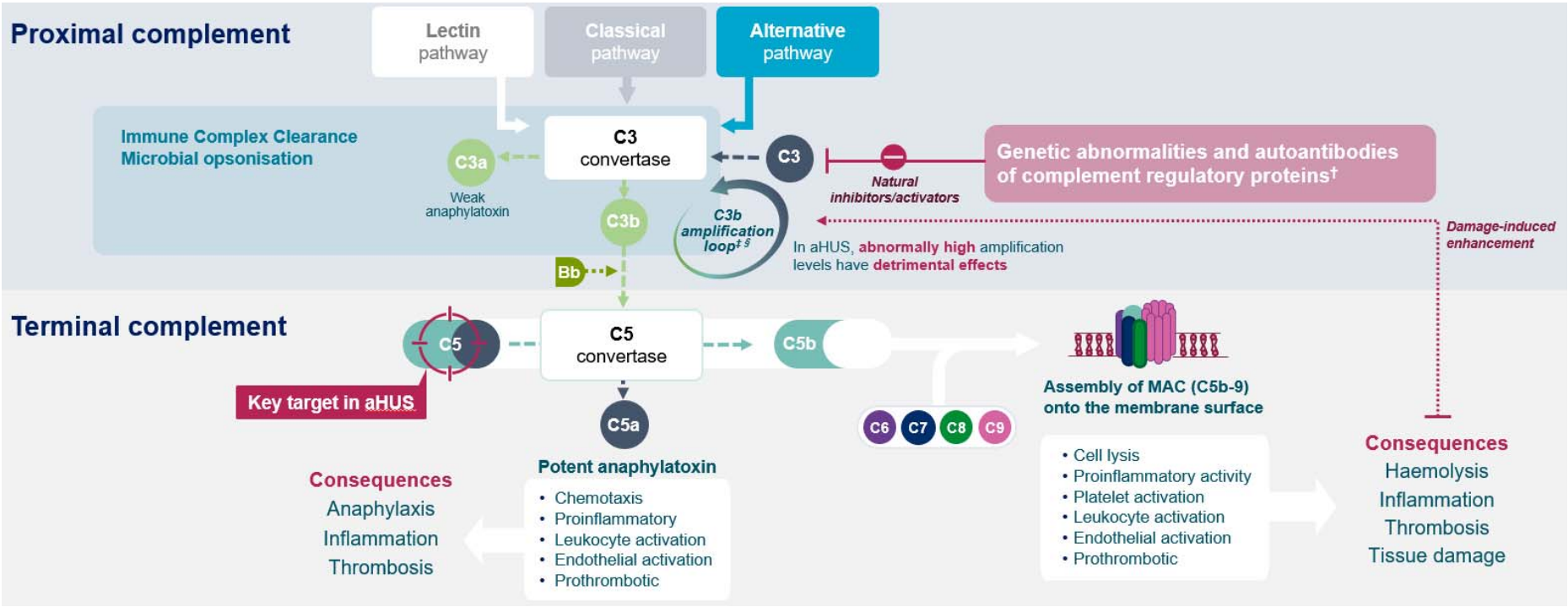
B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Atypical haemolytic uremic syndrome (aHUS) is a life-threatening ultra-rare disease in which patients are susceptible to sudden and progressive episodes of thrombotic microangiopathy (TMA) that can damage vital organs, most commonly the kidneys. [2] It can occur in both adults and children and can develop at any age[3], with most patients presenting with haemolysis, thrombocytopenia, and organ damage typically in the form of acute kidney injury (AKI).[2] Without complement-inhibitor treatment, nearly 80% of patients will die, require renal replacement therapy or have chronic kidney disease (CKD) within 3 years of diagnosis.[4]

The underlying pathophysiology of aHUS is uncontrolled terminal complement activation in the alternative pathway of complement, as depicted in Figure 2. There is no single known cause of this uncontrolled terminal complement activation, and defects in the regulatory components of the complement system can be inherited or acquired.[5] Complement regulatory gene/protein mutations (including Complement Factor H [CFH], Complement Factor I [CFI], Complement Factor B [CFB], membrane cofactor protein [MCP], thrombomodulin [THBD] and C3 mutations), CFH polymorphisms affecting the function of various complement proteins, or anti-CFH autoantibodies are identified in 45–70% of patients.[6-9]

Figure 2: Underlying pathophysiology of TMA in aHUS



Key: CFB, Complement Factor B; CFH, Complement Factor H; CFHR, Complement Factor H-related protein 1; CFI, Complement Factor I; MCP, membrane cofactor protein; THBD, thrombomodulin; TMA, thrombotic microangiopathy.
Notes: †, in aHUS complement dysregulation is caused by mutations in genes such as C3, CFB, CFH, CFI, MCP and THBD, polymorphisms in genes such MCP and CFH, and autoantibodies to CFH[10]; ‡, baseline of activity is continuous; §Cascade of amplification occurs frequently and rapidly (potentially generating >109 C3b molecules in 15 minutes).
Sources: Adapted from Campistol et al. 2015[10]; Kościelska-Kasprzak et al. 2014[11]; Sakari Jokiranta 2017[12]; Maga et al. 2010[13]; Nester 2012.[14]

The true incidence and prevalence of aHUS in the UK are uncertain as aHUS is a diagnosis of exclusion (see Section B.1.3.2) and some patients remain undiagnosed. The National Renal Complement Therapeutics Centre (NRCTC) in Newcastle upon Tyne, where the care of patients with aHUS across England is managed (see Section B.1.3.2) is currently treating [redacted] people for aHUS ([redacted] adult patients and [redacted] paediatric patients) with complement inhibitor (eculizumab), with [redacted] patients started on treatment in the last annual data cut (2019-2020) (data on file).

B.1.3.2 Clinical pathway of care

The National aHUS Service, which operates as part of the NRCTC, manages the diagnosis and treatment of aHUS for NHS England.[15] This follows a decision from the National Institute for Health and Care Excellence (NICE), recommending eculizumab for treating aHUS, only if the following arrangements are in place[16]:

- Coordination of eculizumab use through an expert centre
- Monitoring systems to record the number of people with a diagnosis of aHUS and the number who have eculizumab, and the dose and duration of treatment
- A national protocol for starting and stopping eculizumab for clinical reasons
- A research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur

There is no single diagnostic test for aHUS due to the heterogeneous aetiology (see Section B.1.3.1). aHUS is suspected when patients present with signs of TMA and kidney impairment, and a clinical diagnosis is made once biochemical and haematological analyses have demonstrated microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure and/or renal biopsy shows a thrombotic microangiopathy.[17] Following clinical diagnosis, exclusion of other potential causes of TMA (for example, Shiga toxin-related haemolytic uraemic syndrome [STEC-HUS]) is necessary but in emergency cases, patients can be initiated on complement-inhibitor treatment (currently eculizumab) for aHUS while screening for differential diagnosis continues.[18] The exception to this is that a negative ADAMTS13 test for a differential diagnosis of thrombotic thrombocytopenia purpura (TTP) is a prerequisite for eculizumab initiation in adults. Until the ADAMTS13 test results are available, the NRCTC recommend that plasma therapy is undertaken where

appropriate. In paediatric patients with a clinical diagnosis of aHUS, eculizumab can be initiated before ADAMTS13 test results are available as TTP is rare in children and plasma therapy can be challenging.[18]

Patients without a differential diagnosis continue to be treated with eculizumab and are monitored for renal recovery. Those who do not show signs of renal recovery discontinue treatment on the assumption that these patients do not have complement-mediated aHUS (referred to as non-responders) or have such late presentation of disease that complement-inhibitor treatment is futile (referred to as late-presenters).[19] Typically this occurs after 3–4 months of treatment in current practice[20] but would not occur before 6 months of treatment with ravulizumab, as this is the recommended minimum treatment duration (see Appendix C).

Patients who show signs of renal recovery have historically continued treatment indefinitely; however, discontinuation may be considered for those with stabilization or normalization of renal function in modern practice. Currently in the UK, these patients would be enrolled to the Stopping Eculizumab Treatment Safely in aHUS (SETS) study before discontinuation.[21] This study is designed to assess the safety and impact of eculizumab withdrawal after at least 6 months of treatment in line with this change in practice. Patients who relapse after eculizumab withdrawal will be reinitiated on treatment and are expected to remain on treatment indefinitely.[20] The outcomes of the SETS study will dictate treatment discontinuation and reinitiation decisions in future, that would apply to ravulizumab as well as eculizumab.

Patients initiated on eculizumab treatment who do not show signs of renal recovery due to late presentation may be placed on the kidney transplant list and often receive pre-emptive eculizumab, consisting of a single dose of eculizumab prior to transplant (900 mg for adults, adjusted for body weight in children).[22, 23] Following transplant, patients continue to receive eculizumab treatment and are likely to remain on treatment indefinitely.[23] Ravulizumab is expected to be used in a similar way to eculizumab in transplant patients.[24]

In the treatment initiation phase, adult patients receive eculizumab 900 mg via 25–45 minute intravenous infusion every week for the first four weeks.[25] In the treatment maintenance phase, adult patients receive eculizumab 1,200 mg via 25–45 minute

intravenous infusion every 14 ± 2 days. Paediatric patients with body weight <40 kg receive eculizumab in accordance with the dosing schedule detailed in Table 3.

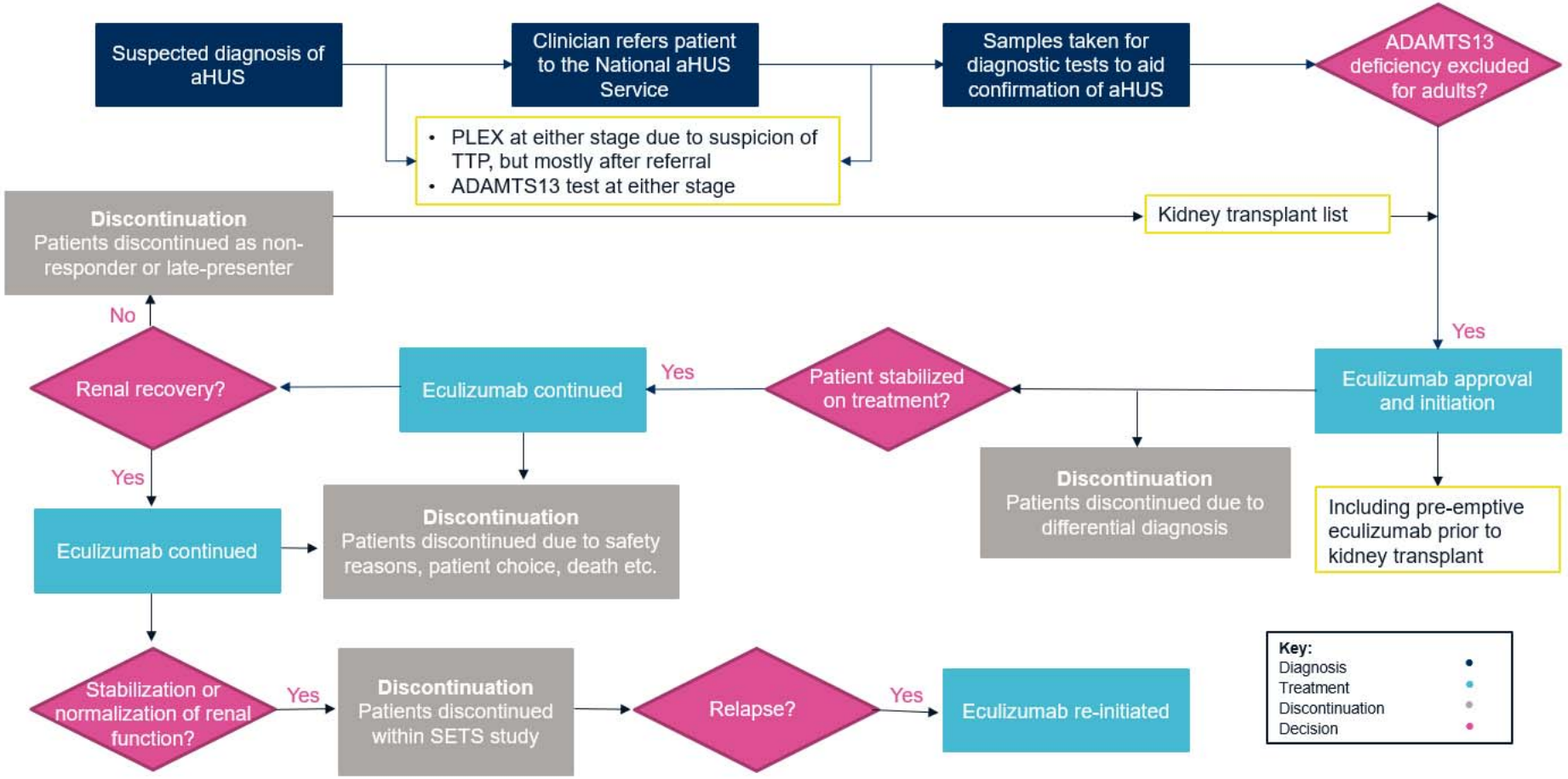
Table 3: Eculizumab dosing regimen for paediatric aHUS patients with body weight below 40 kg

Body weight	Initiation phase	Maintenance phase
30 to <40 kg	600 mg weekly x 2	900 mg at Week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly x 2	600 mg at Week 3; then 600 mg every 2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg at Week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg at Week 2; then 300 mg every 3 weeks
Key: aHUS, atypical haemolytic uremic syndrome. **Source:** Soliris, summary of product characteristics.[25]		

For all patients in England, treatment is initiated by the local nephrology team in the hospital setting. However, once patients are stabilized, treatment can be administered at each patient's home through a homecare service. This homecare service, including the delivery of the drug to the patient's home and the nurse's time needed to mix and infuse the drug, is fully funded by Alexion (only blood tests occasionally requested by the attending nurse are funded by the NHS). In current practice, approximately 75% of patients transfer to the homecare service once it has been determined that they will require ongoing, long-term treatment to manage their condition (data on file).

Figure 3 summarizes the clinical pathway of care for patients with aHUS in NHS England. The proposed positioning for ravulizumab is as an alternative treatment option to eculizumab, with the exception of paediatric patients with body weight below 10 kg who are not covered in the marketing authorization (Table 2).

Figure 3: Clinical pathway of care for patients with aHUS



Key: aHUS, atypical haemolytic uremic syndrome; PLEX, plasma exchange; SETS, Stopping Eculizumab Treatment Safely in aHUS; TTP, thrombotic thrombocytopenic purpura.
Sources: Adapted from the National Renal Complement Therapeutics Centre website.[17, 18, 21, 22]

B.1.3.3 Remaining unmet medical need

Eculizumab has transformed the treatment landscape and prognosis of patients with aHUS, significantly reducing TMA event rates, acute renal failure event rates, progression to end-stage renal disease (ESRD) and mortality rates.[4, 26-31] The latest NRCTC report states that no deaths were attributable to a diagnosis of complement-mediated aHUS or its treatment from April 2018 to March 2019.[19] However, there are some remaining areas of unmet need in the aHUS setting.

Eculizumab is associated with a high administration burden due to its relatively short half-life, with patients requiring bi-weekly infusions to maintain terminal complement inhibition. The 2016 Global aHUS Survey reported that 35% and 29% of patients described venous access and lost school or work time as key concerns related to receiving eculizumab, respectively.[32] Other difficulties of eculizumab treatment include disruption to patients' families, emotional distress related to venous access, travel to receive treatment (for those not receiving homecare), and infection.[32]

Further evidence relating to the burden of treatment with eculizumab derives from another complement-mediated condition, paroxysmal nocturnal haemoglobinuria (PNH). In a series of interviews with patients with PNH and their caregivers in the UK, participants noted the negative effect of bi-weekly infusions of eculizumab on their quality of life.[33] This ranged from anxiety on the day of their infusion, to the impact of travelling, loss of their independence and disruption to their working life.

B.1.4. Equality considerations

No equality issues are anticipated for the appraisal of ravulizumab.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to this appraisal are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

Two pivotal trials provide evidence of the clinical benefits of ravulizumab for the treatment of aHUS: ALXN1210-aHUS-311 and ALXN1210-aHUS-312, as summarized in Table 4. ALXN1210-aHUS-311 provides evidence for the treatment of adult patients and ALXN1210-aHUS-312 provides evidence for the treatment of paediatric patients. Both report outcomes of relevance to the decision problem and are used to populate the subsequent economic modelling.

Table 4: Clinical effectiveness evidence

	ALXN1210-aHUS-311 NCT02949128					**ALXN1210-aHUS-312 NCT03131219**				
Study design	Phase III Single group assignment Open-label					Phase III Single group assignment Open-label				
Population	Adults with aHUS who are complement inhibitor treatment-naïve					Children and adolescents with aHUS who are (i) complement inhibitor treatment-naïve or (ii) clinically stable following ≥90 days treatment with eculizumab				
Intervention(s)	Ravulizumab					Ravulizumab				
Comparator(s)	None					None				
Trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No		No			No	
Rationale for use/non-use in the model	Pivotal evidence of the clinical benefits of ravulizumab in adult patients with aHUS.					Pivotal evidence of the clinical benefits of ravulizumab in paediatric patients with aHUS. Pivotal evidence of the clinical benefits of 'switching' patients clinically stable on eculizumab to ravulizumab.				

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219
Reported outcomes specified in the decision problem	• Response to treatment (complete TMA response, haematological parameters and serum creatinine improvement) • Cessation or avoidance of dialysis (dialysis requirement status) • **Maintenance or improvement of kidney function** (CKD stage, as evaluated by eGFR at select target days) • Development of antibodies and resistance • **Adverse effects of treatment** • **Health-related quality of life**	• Response to treatment (complete TMA response, haematological parameters and serum creatinine improvement) • Cessation or avoidance of dialysis (dialysis requirement status) • **Maintenance or improvement of kidney function** (CKD stage, as evaluated by eGFR at select target days) • Development of antibodies and resistance • **Adverse effects of treatment** • **Health-related quality of life**
Other reported outcomes	• **Treatment exposure** • PK and PD endpoints	• **Treatment exposure** • PK and PD endpoints
Complete published reports	Rondeau et al. 2020[34]	None to date
Conference proceedings	Rondeau et al. 2019[35] Rondeau et al. 2019[36] Cataland et al. 2019[37]	Greenbaum et al. 2019[38] Cataland et al. 2019[37]
Regulatory materials	European Public Assessment Report[39] Summary of Product Characteristics[1]	European Public Assessment Report[39] Summary of Product Characteristics[1]
Clinical study reports	Clinical study report (52-week)[40]	Clinical study report (52-week)[41]

Key: CKD, chronic kidney disease; HRQL, health-related quality of life; LDH, lactate dehydrogenase; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal haemoglobinuria.
Notes: Outcomes in bold are those directly used in the economic modelling.

In the absence of head-to-head data, estimates of the comparative benefits of ravulizumab compared with eculizumab in the aHUS setting are provided through indirect treatment comparison (ITC), described in Section B.2.9. Outcomes of the ITC are supported with head-to-head data formally proving non-inferiority of ravulizumab compared with eculizumab in the PNH setting (see Section B.2.13)

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Table 5 fully details the methodology of ALXN1210-aHUS-311 and ALXN1210-aHUS-312, and each are summarized in turn below.

B.2.3.1 Summary of methodology

B.2.3.1.1 ALXN1210-aHUS-311

ALXN1210-aHUS-311 is a Phase III single-arm trial, designed to assess the efficacy and safety of ravulizumab in adults with a documented diagnosis of aHUS who are complement inhibitor treatment-naïve. Adolescents were also eligible for enrolment to ALXN1210-aHUS-311 but enrolment completed with only adult patients. Consequently, enrolment of adolescents was deferred to ALXN1210-aHUS-312.

Diagnosis of aHUS was based on evidence of TMA (including thrombocytopenia), haemolysis and kidney injury in the absence of ADAMTS13 deficiency (which confirms a differential diagnosis of TTP), Shiga toxin (which confirms a differential diagnosis of Shiga-toxin producing *Escherichia coli*-HUS [STEC-HUS]), a positive direct Coombs test (which confirmed a differential diagnosis of autoimmune haemolytic anaemia [AIHA]) or systemic bacterial infection that could confound an accurate diagnosis of aHUS (in the investigator's opinion). There were no restrictions on enrolment based on kidney transplant status or dialysis status, except for chronic dialysis needs. Patients with onset of TMA post-partum were eligible if they showed persistent evidence of TMA for >3 days after the day of childbirth.

The study consisted of a Screening Period of up to 7 days, a 26-week Initial Evaluation Period and an Extension Period of up to 4.5 years (or until the product is registered or approved). Data are currently available up to 2 July 2019 when all patients had received at least 52 weeks of treatment. The primary efficacy endpoint was complete TMA response during the Initial Evaluation Period. Strict criteria were used to define complete TMA response, encompassing simultaneous normalization of haematologic parameters (platelet count and lactate dehydrogenase [LDH]) and ≥25% improvement in serum creatinine at two separate assessments obtained at least 4 weeks (28 days) apart (and any measurement in-between).

B.2.3.1.2 ALXN1210-aHUS-312

ALXN1210-aHUS-312 is a Phase III single-arm trial, designed to assess the efficacy and safety of ravulizumab in children and adolescents with a documented diagnosis of aHUS. The trial includes two cohorts: Cohort 1 enrolled complement inhibitor treatment-naïve patients and Cohort 2 enrolled patients clinically stable following at least 90 days of eculizumab treatment (eculizumab-experienced patients).

Diagnosis of aHUS was based on the same evidence of TMA in the absence of differential diagnosis test results as described for ALXN1210-aHUS-311, and the trial used the same primary efficacy endpoint. Study periods were also aligned except for the Screening Period for Cohort 2 that could continue for up to 28 days. Data are currently available up to 3 December 2019 when all patients had received at least 52 weeks of treatment.

Table 5: Methodology of ALXN1210-aHUS-311 and ALXN1210-aHUS-312

	ALXN1210-aHUS-311 **NCT02949128**	**ALXN1210-aHUS-312** **NCT03131219**
Trial design	Phase III, open-label, single arm, multi-centre study 41 sites across 14 countries (including the UK where [redacted] patients were recruited across [redacted] sites) The study consists of a: • Screening Period of up to 7 days • Initial Evaluation Period of 26 weeks • Extension Period of up to 4.5 years	Phase III, open-label, single arm, multi-centre study 20 sites across eight counties (including the UK where [redacted] patients were recruited across [redacted] sites) The study consists of a: • Screening Period of up to 7 days for Cohort 1 or up to 28 days for Cohort 2 • Initial Evaluation Period of 26 weeks • Extension Period of up to 4.5 years
Inclusion criteria	1. Male or female patients aged 12 or older, weighing ≥40 kg at the time of consent 2. Evidence of TMA (including thrombocytopenia, evidence of haemolysis, and kidney injury) based on: – Platelet count < 150,000/μL at screening – LDH ≥ 1.5 × ULN and Hb ≤ LLN for age and gender at screening – Serum creatinine level ≥ ULN in adults or ≥ 97.5th percentile for age 3. Among patients with a kidney transplant: – Known history of aHUS prior to current kidney transplant, or – No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen	1. Male or female patients aged <18 years, weighing ≥5 kg at the time of consent, who: – For Cohort 1 patients, had not been previously treated with complement inhibitors – For Cohort 2 patients, were between 12 and < 18 years of age (non-Japanese sites) or < 18 years of age (Japanese sites) and had been treated with eculizumab according to the labelled dosing recommendation for aHUS for at least 90 days prior to screening 2. For Cohort 1 patients, evidence of TMA (including thrombocytopenia, evidence of haemolysis, and kidney injury) based on: – Platelet count < 150,000/μL at screening – LDH ≥ 1.5 × ULN and Hb ≤ LLN for age and gender at screening – Serum creatinine level ≥ 97.5th percentile for age

	4. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth 5. Patients vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who received the meningococcal vaccine less than 2 weeks before initiating ravulizumab treatment must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ravulizumab treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination 6. Patients < 18 years of age must have been vaccinated against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines 7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug. 8. Patients must have been willing and able to give written informed consent and to comply with all study visits and procedures. For patients < 18 years of age, patient's legal guardian must have been willing and able to give written informed consent and the patient must have been willing to give written informed assent	3. For Cohort 2 patients, documented diagnosis of aHUS, including increase in LDH > ULN, increase in creatinine > ULN, and decrease in platelets < LLN at the time of the TMA event 4. For Cohort 2 patients, clinical evidence of response to eculizumab indicated by stable TMA parameters at screening, including: – Platelet count ≥ 150,000/μL, and – LDH < 1.5 × ULN, and – eGFR > 30 mL/min/1.73 m^2 5. Among patients with a kidney transplant: – Known history of aHUS prior to current kidney transplant, or – No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen 6. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth 7. Patients vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who received the meningococcal vaccine less than 2 weeks before initiating ravulizumab treatment must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ravulizumab treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination. 8. Patients must have been vaccinated against *Haemophilus influenzae* type b and *Streptococcus*

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		pneumoniae according to national and local vaccination schedule guidelines 9. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug. 10. Patient's legal guardian must have been willing and able to give written informed consent and the patient must have been willing to give written informed assent and comply with the study visit schedule
Exclusion criteria	1. Known familial or acquired ADAMTS13 deficiency 2. Known STEC-HUS 3. Positive direct Coombs test 4. Known HIV infection 5. Unresolved meningococcal disease 6. Confirmed diagnosis of ongoing sepsis within 7 days prior to the start of screening 7. Presence or suspicion of active and untreated systemic bacterial infection that confounded an accurate diagnosis of aHUS or impeded the ability to manage the aHUS disease 8. Pregnancy or breastfeeding 9. Heart, lung, small bowel, pancreas, or liver transplant 10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of AMR	1. Known familial or acquired ADAMTS13 deficiency 2. Known STEC-HUS 3. Positive direct Coombs test 4. Known HIV infection 5. Unresolved meningococcal disease 6. Confirmed diagnosis of ongoing sepsis within 7 days prior to the start of screening 7. Presence or suspicion of active and untreated systemic bacterial infection that confounded an accurate diagnosis of aHUS or impeded the ability to manage the aHUS disease 8. Females who planned to become pregnant during the study or were currently pregnant or breastfeeding 9. Heart, lung, small bowel, pancreas, or liver transplant 10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of AMR

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	11. Among patients without a kidney transplant, history of kidney disease other than aHUS	11. Among patients without a kidney transplant, history of kidney disease other than aHUS
	12. Identified drug exposure-related HUS	12. Identified drug exposure-related HUS
	13. Received plasma exchange/plasma infusion, for 28 days or longer, prior to the start of screening for the current TMA	13. For Cohort 1, patients who received plasma exchange/plasma infusion, for 28 days or longer, prior to the start of screening for the current TMA
	14. History of malignancy within 5 years of screening except for nonmelanoma skin cancer or carcinoma in situ of the cervix that had been treated with no evidence of recurrence	14. History of malignancy within 5 years of screening except for nonmelanoma skin cancer or carcinoma in situ of the cervix that had been treated with no evidence of recurrence
	15. Bone marrow transplant/hematopoietic stem cell transplant within the last 6 months prior to the start of Screening	15. Bone marrow transplant/hematopoietic stem cell transplant within the last 6 months prior to the start of Screening
	16. HUS related to known genetic defects of cobalamin C metabolism	16. HUS related to known genetic defects of cobalamin C metabolism
	17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome	17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome
	18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD)	18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD)
	19. Chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of screening, unless for unrelated medical condition; or chronic rituximab therapy within 12 weeks prior to the start of screening	19. Chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of screening, unless for unrelated medical condition; or chronic rituximab therapy within 12 weeks prior to the start of screening
	20. Patients who received other immunosuppressive therapies unless part of an established post-transplant antirejection regimen, the patient had confirmed anti-complement factor antibodies requiring	20. Patients who received other immunosuppressive therapies unless part of an established post-transplant antirejection regimen, the patient had confirmed anti-complement factor antibodies requiring

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	immunosuppressive therapy, or steroids were being used for a condition other than aHUS 21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever was greater 22. Prior use of eculizumab or other complement inhibitors 23. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins 24. Any medical or psychological condition that could have increased the risk to the patient by participating in the study or confound the outcome of the study 25. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening 26. Use of tranexamic acid within 7 days prior to screening	immunosuppressive therapy, or steroids were being used for a condition other than aHUS 21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever was greater 22. For Cohort 1, prior use of eculizumab or other complement inhibitors 23. For Cohort 2, prior use of complement inhibitors other than eculizumab 24. For Cohort 2, any known abnormal TMA parameters within 90 days prior to screening 25. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins 26. Any medical or psychological condition that could have increased the risk to the patient by participating in the study or confound the outcome of the study 27. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening 28. Use of tranexamic acid within 7 days prior to screening

<table>
<tr><th></th><th>ALXN1210-aHUS-311
NCT02949128</th><th>ALXN1210-aHUS-312
NCT03131219</th></tr>
<tr><td>Trial drugs</td><td>Ravulizumab (n=58): Loading dose was given on Day 1 with maintenance doses on Day 15 and Q8W thereafter by IV infusion. Dosages were based on the patient's body weight as shown below:
<table>
<tr><th>Body weight</th><th>Ravulizumab loading dose</th><th>Ravulizumab maintenance dose</th></tr>
<tr><td>≥40 to <60 kg</td><td>2,400 mg</td><td>3,000 mg</td></tr>
<tr><td>≥60 to <100 kg</td><td>2,700 mg</td><td>3,300 mg</td></tr>
<tr><td>≥100 kg</td><td>3,000 mg</td><td>3,600 mg</td></tr>
</table></td><td>Ravulizumab Cohorts 1 (n=21) and 2 (n=10): Loading dose was given on Day 1 with maintenance doses on Day 15 and Q8W thereafter for patients weighing ≥ 20 kg, or Q4W for patients weighing < 20 kg by IV infusion. For Cohort 2 patients, Day 1 of study treatment occurred 14 days from the patient's last dose of eculizumab. Dosages were based on the patient's body weight as shown below:
<table>
<tr><th>Body weight</th><th>Ravulizumab loading dose</th><th>Ravulizumab maintenance dose (frequency)</th></tr>
<tr><td>≥5 to <10 kg</td><td>600 mg*</td><td>300 mg (Q4W)</td></tr>
<tr><td>≥10 to <20 kg</td><td>600 mg</td><td>600 mg (Q4W)</td></tr>
<tr><td>≥20 to <30 kg</td><td>900 mg</td><td>2,100 mg (Q8W)</td></tr>
<tr><td>≥30 to <40 kg</td><td>1,200 mg</td><td>2,700 mg (Q8W)</td></tr>
<tr><td>≥40 to <60 kg</td><td>2,400 mg</td><td>3,000 mg (Q8W)</td></tr>
<tr><td>≥60 to <100 kg</td><td>2,700 mg</td><td>3,300 mg (Q8W)</td></tr>
<tr><td>≥100 kg</td><td>3,000 mg</td><td>3,600 mg (Q8W)</td></tr>
</table>
*loading dose of 300 mg in the ≥ 5 to < 10 kg group was used for patients enrolled prior to a protocol amendment</td></tr>
<tr><td>Permitted and disallowed concomitant medications</td><td>Patients were prohibited from receiving any of the following medications and procedures at any time after the first dose of study drug for all patients in the study until completion of the study or early termination of the patient from the study:
Eculizumab or other complement inhibitors
Use of any other investigational drug or device as part of a clinical study
IVIg (unless for an unrelated medical need)</td><td>Patients were prohibited from receiving any of the following medications and procedures at any time after the first dose of study drug for all patients in the study until completion of the study or early termination of the patient from the study:
Eculizumab or other complement inhibitors
Use of any other investigational drug or device as part of a clinical study
IVIg (unless for an unrelated medical need)</td></tr>
</table>

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	• Rituximab • Plasma exchange/plasma infusion • New dialysis within the first 48-hour period following the first dose of ravulizumab unless there was a compelling medical need Use of other immunosuppressive therapies (such as steroids, mTORi, CNI) during the study were not allowed unless: a) part of an established post-transplant antirejection regimen, or b) patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or c) steroids were being used for a condition other than aHUS, or d) steroids initiated empirically prior to enrolment and were being tapered as standard of care. Corticosteroid use for empiric treatment of indications including 'thrombotic microangiopathy,' 'renal failure standard of care,' or 'prevention of systemic disease' prior to or during screening was not exclusionary or prohibited.	• Rituximab • Plasma exchange/plasma infusion • New dialysis within the first 48-hour period following the first dose of ravulizumab unless there was a compelling medical need Use of other immunosuppressive therapies (such as steroids, mTORi, CNI) during the study were not allowed unless: a) part of an established post-transplant antirejection regimen, or b) patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or c) steroids were being used for a condition other than aHUS, or d) steroids initiated empirically prior to enrolment and were being tapered as standard of care.
Primary efficacy outcome	• Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of haematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from BL sustained for at least 2 consecutive measures over a period of at least 4 weeks	• Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of haematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from BL sustained for at least 2 consecutive measures over a period of at least 4 weeks (Cohort 1)
Secondary efficacy outcomes	• Time to Complete TMA Response • Complete TMA Response status over time • Dialysis requirement status at endpoint • Observed value and change from baseline in eGFR	• Time to Complete TMA Response (Cohort 1) • Complete TMA Response status over time (Cohort 1) • Dialysis requirement status at endpoint (both cohorts)

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	• CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline • Observed value and change from baseline in haematological parameters (platelets, LDH, Hb) • Increase in Hb of ≥ 20 g/L from baseline • Change from baseline in QoL, as measured by EQ-5D-3L and FACIT-Fatigue • TMA parameters in patients who discontinued treatment but remained in the study	• Observed value and change from baseline in eGFR (both cohorts) • CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline (both cohorts) • Observed value and change from baseline in haematological parameters (platelets, LDH, Hb) (both cohorts) • Increase in Hb of ≥ 20 g/L from baseline (Cohort 1) • Change from baseline in QoL, as measured by Paediatric FACIT-Fatigue (patients ≥ 5 years of age) (both cohorts) • TMA parameters in patients who discontinued treatment but remained in the study (Cohort 1)
Safety and PK/PD outcomes	The long-term safety and tolerability of ravulizumab was evaluated by: • Physical examinations • Vital signs • Electrocardiograms • Laboratory assessments • Incidence of AEs and SAEs • The proportion of patients who developed ADAs PK/PD endpoints: • Changes in serum ravulizumab concentration over time • Changes in serum free C5 concentrations over time	The long-term safety and tolerability of ravulizumab was evaluated by: • Physical examinations • Vital signs • Electrocardiograms • Laboratory assessments • Incidence of AEs and SAEs • The proportion of patients who developed ADAs PK/PD endpoints: • Changes in serum ravulizumab concentration over time • Changes in serum free C5 concentrations over time

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219
	• Changes in serum free C5 and ravulizumab concentration in patients who discontinued treatment but remained in the study	• Changes in serum free C5 and ravulizumab concentration in patients who discontinued treatment but remained in the study

Key: ADAs, antidrug antibodies; AEs, adverse events; aHUS, atypical haemolytic uremic syndrome; AMR, acute antibody-mediated rejection; BL, baseline; C5, component 5; CI, confidence interval; CKD, chronic kidney disease; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol 5-Dimension 3-Level; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; Hb, haemoglobin; HIV, human immunodeficiency virus; HUS, haemolytic uremic syndrome; IV, intravenous; KM, Kaplan–Meier; LDH, lactate dehydrogenase; LLN, lower limit of normal; mTORi, mammalian target of rapamycin inhibitor; PD, pharmacodynamics; PK, pharmacokinetics; PP, per protocol; Q4W, every 4 weeks; Q8W, every 8 weeks; QoL, quality of life; SAEs, serious adverse events; SD, standard deviation; STEC-HUS, Shiga toxin-related haemolytic uremic syndrome; TMA, thrombotic microangiopathy; ULN, upper limit of normal.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]

B.2.3.2 Baseline characteristics

Table 6 summarizes the demographic and clinical characteristics of patients in the full analysis set (FAS) of ALXN1210-aHUS-311 and ALXN1210-aHUS-312, defined as patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level ≥ upper limit of normal (ULN) during screening and had no known familial or acquired ADAMTS13 deficiency or STEC-HUS.

Differences observed across trials and cohorts were expected a priori with more severe disease characteristics displayed in complement inhibitor treatment-naïve patients. Most patients in this group (complement inhibitor treatment-naïve) had laboratory values outside of normal ranges at baseline and substantially impaired kidney function, manifesting in a high proportion of patients requiring dialysis prior to study enrolment and presenting with CKD stage ≥4. In comparison, eculizumab experienced patients enrolled to ALXN1210-aHUS-312 Cohort 2 had laboratory values within normal ranges at baseline and normal kidney function with most patients presenting with CKD stage 1.

Generalizability of these baseline characteristics to the UK patient population and potential direction of bias resulting from differences is discussed in Section B.2.13. Overarching observations are that there is a high proportion of Asian patients in the trial populations, and a lower proportion of patients with a known pathogenic variant or autoantibody in the trial populations than expected in patients treated with complement-inhibitor in UK clinical practice.[24] Very few patients ([redacted]) were <10 kg in weight across trials, as reflected by the exclusion of these patients in the final marketing authorization (Table 2).

Table 6: Baseline characteristics of patients in ALXN1210-aHUS-311 and ALXN1210-aHUS-312

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Male, n (%)	19 (33.9)	8 (44.4)	9 (90.0)
Race, n (%)			
White/Caucasian	29 (51.8)	9 (50.0)	5 (50.0)
Asian	15 (26.8)	5 (27.8)	4 (40.0)
Undisclosed	8 (14.3)	1 (5.6)	0
Other	4 (7.1)	4 (22.2)	1 (10.0)
Age at time of first aHUS symptoms			
Median years (range)	40.1 (9.3–76.6)	[redacted]	[redacted]
Age at first infusion of study drug			
Median years (range)	40.1 (19.5–76.6)	[redacted]	12.5 (1.2–15.5)
<2 years, n (%)	0	2 (11.1)	1 (10.0)
2 to <6 years, n (%)	0	9 (50.0)	1 (10.0)
6 to <12 years, n (%)	0	5 (27.8)	1 (10.0)
12 to <18 years, n (%)	0	2 (11.1)	7 (70.0)
18 to <30 years, n (%)	11 (19.6)	0	0
30 to <40 years, n (%)	17 (30.4)	0	0
40 to <50 years, n (%)	15 (26.8)	0	0
50 to <60 years, n (%)	5 (8.9)	0	0
≥60 years, n (%)	8 (14.3)	0	0
Weight at first infusion of study drug	[redacted]		
Median kg (range)	[redacted]	[redacted]	47.8 (9–69)
<10 kg	[redacted]	[redacted]	[redacted]
10 to <20 kg	[redacted]	[redacted]	[redacted]
20 to <30 kg	[redacted]	[redacted]	[redacted]
30 to <40 kg	[redacted]	[redacted]	[redacted]
40 to <60 kg	[redacted]	[redacted]	[redacted]
60 to <100 kg	[redacted]	[redacted]	[redacted]
≥100 kg	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Platelets (normal: 130–400 10^9/L)			281.8
Median x 10^9/L (range)	95.3 (18–473)	51.3 (14–125)	(207–416)
LDH (normal: 120–246 U/L)		1,963	
Median U/L (range)	508 (230–3,249)	(772–4,985)	207 (139–356)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Serum creatinine Median µmol/L (range)	n=58[a] 284 (51–1,027)	Not available	Not available
Haemoglobin (normal: 130–175 g/L) Median g/L (range)	85 (60.5–140)	74.3 (32–106)	132 (115–148)
eGFR (normal: ≥ 60 mL/min/1.73 m^2) Median mL/min/1.73 m^2 (range)	10 (4–80)	22 (10–84)	100 (54–137)
Dialysis within 5 days of first dose n (%)	29 (51.8)	6 (33.3)	0
Kidney transplant prior to enrolment Any transplant, n (%) Related to aHUS, n (%)	8 (14.3) [redacted]	1 (5.6) [redacted]	1 (10.0) [redacted]
Onset of TMA post-partum, n (%)	8 (14.3)	[redacted]	[redacted]
CKD stage, n (%) 1 2 3A 3B 4 5 Missing	n=54 0 3 (5.4) 1 (1.8) 2 (3.6) 9 (16.1) 40 (71.4) 1 (1.8)	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 8 (80.0) 1 (10.0) 1 (10.0) 0 0 0 0
Systolic blood pressure, mmHg Median (range)	[redacted] [redacted]	[redacted] [redacted]	 [redacted]
Patients with ≥1 known pathogenic variant or autoantibody, n (%) C3 CD46 CFB CFH CFH autoantibody	n=39 8 (20.5) 1 (2.6) 2 (5.1) 1 (2.6) 2 (5.1) 2 (5.1)	n=10 2 (20.0)	Not available
Extra-renal signs or symptoms Cardiovascular, n (%) Pulmonary, n (%) Central nervous system, n (%) Gastrointestinal, n (%) Skin, n (%) Skeletal muscle, n (%)	 39 (69.6) 25 (44.6) 29 (51.8) 35 (62.5) 17 (30.4) 13 (23.2)	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 1 (10.0) 0 0 0 0 0

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Medical history prior to study[b], n (%) Hypertension Acute kidney injury Headache Renal failure Nausea Constipation	[redacted]	[redacted]	[redacted]
PE/PI before first dose of study drug and related to current TMA, n (%)	n=54 48 (82.8)	[redacted]	[redacted]
Hospitalization history prior to study Emergency room visit, n (%) Other hospitalization, n (%) ICU stay, n (%)	[redacted]	[redacted]	[redacted]
Length of ICU stay N Median days (range)	[redacted]	[redacted]	[redacted]
FACIT-Fatigue score[c] at baseline Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]
EQ-5D-3L score[d] at baseline Mean VAS (SD) Mean TTO (SD)	[redacted]	Not collected	Not collected

Key: aHUS, atypical haemolytic uremic syndrome; C3, Complement 3; CD46, cluster of differentiation 46; CFB, Complement Factor B; CFH, Complement Factor H; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; ICU, intensive care unit; LDH, lactate dehydrogenase; PE, plasma exchange; PI, plasma infusion; SD, standard deviation; TMA, thrombotic microangiopathy, TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], data reported for the safety set; [b], reported in >20% of patients – dashes represent this criteria not being met in individual trials/cohorts; [c], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [d], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]; EMA Variation Assessment Report[39]; Rondeau et al. 2020.[34]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis

Table 7 fully details the statistical analysis and analysis sets in ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

The primary population for efficacy analyses in both trials was the FAS. Safety analyses were conducted on patients who received at least one dose of ravulizumab.

Table 7: Statistical analysis in ALXN1210-aHUS-311 and ALXN1210-aHUS-312

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**
Primary objective	To assess the efficacy of ravulizumab in complement inhibitor treatment-naïve adult patients with aHUS to inhibit complement-mediated TMA as characterized by thrombocytopenia, haemolysis, and renal impairment.	To assess the efficacy of ravulizumab in complement inhibitor treatment-naïve paediatric patients with aHUS to inhibit complement-mediated TMA as characterized by thrombocytopenia, haemolysis, and renal impairment.
Statistical testing	• Complete TMA response: point estimate and a 95% CI for the proportion of complete TMA responders in ravulizumab-treated patients. The 95% CI was based on the asymptotic Gaussian approximation method with a continuity correction. • For time to event analyses, a KM cumulative distribution curve was generated along with a 2-sided 95% CI; for dichotomous variables (dialysis status, CKD stage) a 2-sided 95% CI was provided. • Descriptive statistics for continuous variables (eGFR, platelets, LDH, Hb, HRQL) were used to summarize the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates was fit to test whether	• Complete TMA response in Cohort 1: point estimate and a 95% CI for the proportion of complete TMA responders in ravulizumab-treated patients. The 95% CI was based on exact confidence limits using the Clopper-Pearson method. • For time to event analyses, a KM cumulative distribution curve was generated along with a 2-sided 95% CI; for dichotomous variables (dialysis status, CKD stage) a 2-sided 95% CI was provided. • Descriptive statistics for continuous variables (eGFR, platelets, LDH, Hb, HRQL) were used to summarize the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates was fit to test whether

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219
	changes differ from zero at each time point. • Safety analyses were presented using descriptive statistics. No formal hypothesis testing was performed for the safety parameters.	changes differ from zero at each time point. • Safety analyses were presented using descriptive statistics. No formal hypothesis testing was performed for the safety parameters.
Power calculation	Approximately 55 patients were planned to be enrolled to the trial to yield at least 50 evaluable patients by Day 183. This sample size was deemed appropriate to provide complete safety information and the necessary precision level for the planned estimation. The sample size was increased to 55 patients to account for a potential 10% dropout rate.	The original protocol had a planned sample size of 16 patients. This sample size was deemed appropriate to get proper representation in each of the 4 planned age groups (birth to < 2 years, 2 to < 6 years, 6 to < 12 years, 12 to < 18 years) and provide adequate safety information and precision level for the planned estimation. The total planned sample size was increased to include approximately 23 to 28 patients to account for the addition of Cohort 2 in a protocol-amendment.
Analysis sets	**FAS:** primary population for efficacy analyses – included all patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level ≥ ULN during screening and had no known familial or acquired ADAMTS13 deficiency or STEC-HUS. **PP:** sensitivity population for efficacy analyses – included patients in the FAS who met the following criteria: – Received 100% of the planned number of infusions during the 26-week Initial Evaluation Period – Did not take any prohibited medications or undergo any prohibited procedures – Met Inclusion Criteria 2 and 8 – Did not meet Exclusion Criteria 3, 7, 10–13, 15–18, 21, 22 or 26 **Safety:** population for all safety analyses – included all patients who	**FAS:** primary population for efficacy analyses – included all patients who received at least one dose of ravulizumab and had at least one efficacy assessment, and in the case of Cohort 1, a serum creatinine level ≥97.5th percentile for age during screening and had no known familial or acquired ADAMTS13 deficiency or STEC-HUS. **PP:** sensitivity population for efficacy analyses – included patients in the FAS who met the following criteria: – Received 100% of the planned number of infusions during the 26-week Initial Evaluation Period – Did not take any prohibited medications or undergo any prohibited procedures – Met Inclusion Criteria 2 and 10 in the case of Cohort 1 or Criteria 3, 4 and 10 in the case of Cohort 2

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219
	received at least one dose of ravulizumab.	– Did not meet Exclusion Criteria 3, 10–13, 15–18, 21, 22 or 28 in the case of Cohort 1 or Criteria 3, 10–12, 15–18, 21, 23, 24 or 28 in the case of Cohort 2 **Safety:** population for all safety analyses – included all patients who received at least one dose of ravulizumab.
Missing data	• Patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their LOCF. • A confirmatory result could not be from an assessment that was carried forward from the initial assessment when all Complete TMA Response criteria were met. • Complete TMA Response in patients who withdrew from the study prior to Week 26 was assessed based on their data up to the time of withdrawal.	• Patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their LOCF. • A confirmatory result could not be from an assessment that was carried forward from the initial assessment when all Complete TMA Response criteria were met. • Complete TMA Response in patients who withdrew from the study prior to Week 26 was assessed based on their data up to the time of withdrawal.

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; Hb, haemoglobin; HRQL, health-related quality of life; KM, Kaplan–Meier; LDH, lactate dehydrogenase; LOCF, last observation carried forward; MMRM, mixed model for repeated measures; PP, per protocol; STEC-HUS, Shiga toxin-related haemolytic uremic syndrome; TMA, thrombotic microangiopathy; ULN, upper limit of normal.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]

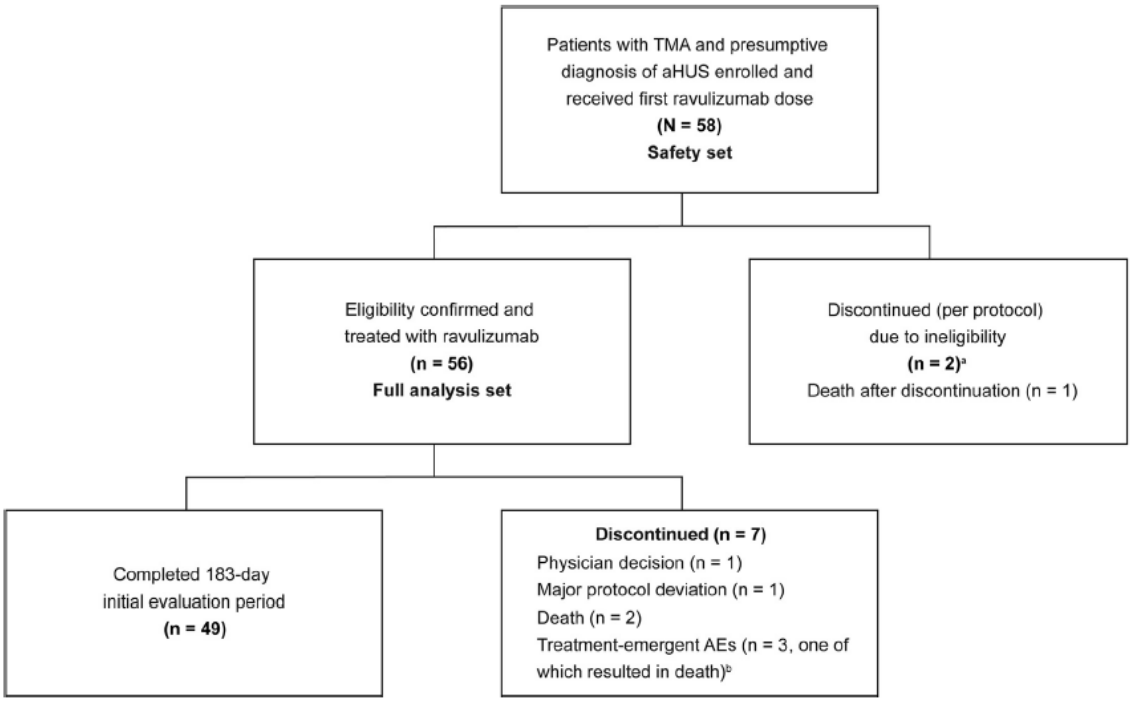
B.2.4.2 Patient disposition data

B.2.4.2.1 ALXN1210-aHUS-311

Figure 4 summarizes patient disposition data up to Extension Period entry.

A total of 58 patients were enrolled to the ALXN1210-aHUS-311 trial and received one or more doses of ravulizumab. Two patients discontinued after the first dose because of differential diagnosis (they both tested positive for STEC-HUS). Of the remaining 56 patients, 49 completed the Initial Evaluation Period.

Figure 4: Participant flow in ALXN1210-aHUS-311 (up to Extension Period)



Key: AE, adverse event; aHUS, atypical haemolytic uremic syndrome; TMA, thrombotic microangiopathy.
Notes: [a], both patients discontinued due to a positive test for Shiga toxin – producing *Escherichia coli*; [b], Treatment-emergent AEs leading to study discontinuation were autoimmune haemolytic anaemia, intracranial haemorrhage (resulting in patient death), and immune thrombocytopenic purpura. Major protocol deviation was the receipt of plasma exchange.
Source: Rondeau et al. 2020.[34]

As of data cut-off (2 July 2019), [redacted] patients continue to be treated with ravulizumab in the Extension Period; [redacted] further patients continue to be monitored without study treatment.[40] The most common reason for discontinuation in the Extension Period was physician or patient choice (n=[redacted]), which was most frequently made due to complete TMA response and low risk of disease recurrence/relapse (n=[redacted] including [redacted] patients who had onset of TMA post-partum) (data on file). Participant flow up to data cut-off is provided in Appendix D.

B.2.4.2.2 ALXN1210-aHUS-312

A total of [redacted] patients were enrolled to Cohort 1 of the ALXN1210-aHUS-312 trial and received one or more doses of ravulizumab.[41] Three patients discontinued after one

or two doses because of differential diagnosis ([redacted] tested positive for STEC-HUS) or failure to meet the eligibility criteria for laboratory values. Of the remaining [redacted] patients, [redacted] completed the Initial Evaluation Period with [redacted] discontinuing due to an adverse event (AE). As of data cut-off (3 December 2019), [redacted] patients continue to be treated with ravulizumab in the Extension Period with one patient discontinuing due to physician choice. Participant flow up to data cut-off is provided in Appendix D.

A total of [redacted] patients were enrolled to Cohort 2 of the ALXN1210-aHUS-312 trial; all patients completed the Initial Evaluation Period and continue to be treated in the Extension Period as of data cut-off (3 December 2019).[41]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The complete quality assessment for ALXN1210-aHUS-311 and ALXN1210-aHUS-312 is provided in Appendix D.

Both trials were conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, and trial protocols were approved by the institutional review board or independent ethics committee at each participating site.

Although open-label in design, each complete TMA response outcome measure (which made up the primary endpoint of both trials) was objectively assessed at a central laboratory and therefore the lack of blinding is not expected to affect the results of the study. The primary analysis population was pre-defined as the FAS rather than an intention-to-treat (ITT) population: this included all patients who received at least one dose of treatment and a clinical diagnosis of aHUS with exclusion of other potential causes of TMA, reflecting the indication of relevance to this appraisal.

A randomized controlled trial in patients with aHUS was not deemed feasible within a reasonable time frame given the rarity of the disease. As such, regulatory agencies agreed to the single-arm design adopted but the lack of comparative efficacy is a

limitation of the ravulizumab evidence base. There are also some differences observed in the patients enrolled to ALXN1210-aHUS-311 and ALXN1210-aHUS-312 compared with those treated with complement-inhibitor treatment in UK clinical practice. These are discussed in Section B.2.13, but importantly would bias against ravulizumab, such that trial outcomes can be considered a conservative estimate of the true treatment effect.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 Initial Evaluation Period

Table 8 provides an overview of efficacy results for the FAS population. Primary and secondary outcomes of interest to the decision problem are summarized for each trial in turn below. PP population analyses are provided in Appendix L.

Table 8: Summary of efficacy results from ALXN1210-aHUS-311 and ALXN1210-aHUS-312: Initial Evaluation Period (FAS)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Complete TMA response, n (%) [95% CI]	30 (53.6) [39.6–67.5]	14 (77.8) [52.4–93.6]	Not relevant
Platelet count normalization, n (%) [95% CI]	47 (83.9) [73.4–94.4]	17 (94.4) [72.7–99.9]	Platelet count remained stable
Change in platelet count, Median x10^9/L (range)	125 (-126, 338)	247 [redacted]	[redacted]
LDH normalization, n (%) [95% CI]	43 (76.8) [64.8–88.7]	16 (88.9) [65.3–98.6]	LDH remained stable
Change in LDH, Median U/L (range)	-310.8 (-3,072, 9)	-1,851.5 [redacted]	[redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	33 (58.9) [45.2–72.7]	[redacted]	Not relevant
Haematologic normalization[a], n (%) [95% CI]	41 (73.2) [60.7–85.7]	16 (88.9) [65.3–98.6]	Not relevant

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Haemoglobin response[b], n (%) [95% CI]	40 (71.4) [69.1–91.7]	16 (88.9) [65.3–98.6]	Hb remained stable
Change in haemoglobin, Median g/L (range)	35 (9, 69)	[redacted]	[redacted]
Time to complete TMA response, median days (95% CI)	86.0 ([redacted])	[redacted]	Not relevant
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	[redacted]	108 [redacted]	[redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	29 (-13, 108)	80 [redacted]	[redacted]
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline, n/N (%)	17/29 (58.6) 6/27 (22.2)[c]	[redacted]	Not relevant [redacted]
CKD stage improvement, n/N (%)	32/47 (68.1)	15/17 (88.2)	[redacted]
CKD stage worsening, n/N (%)	2/47 (4.3)	0/17 (0.0)	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	20.0 (-16, 48) [redacted]	10.0 [redacted] [redacted]	[redacted] [redacted]
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	37/44 (84.1)	[redacted]	Not relevant
Change in EQ-5D-3L score[e], Mean VAS (SD) (n=45) Mean TTO (SD) (n=46)	[redacted] [redacted]	Not collected	Not collected

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.

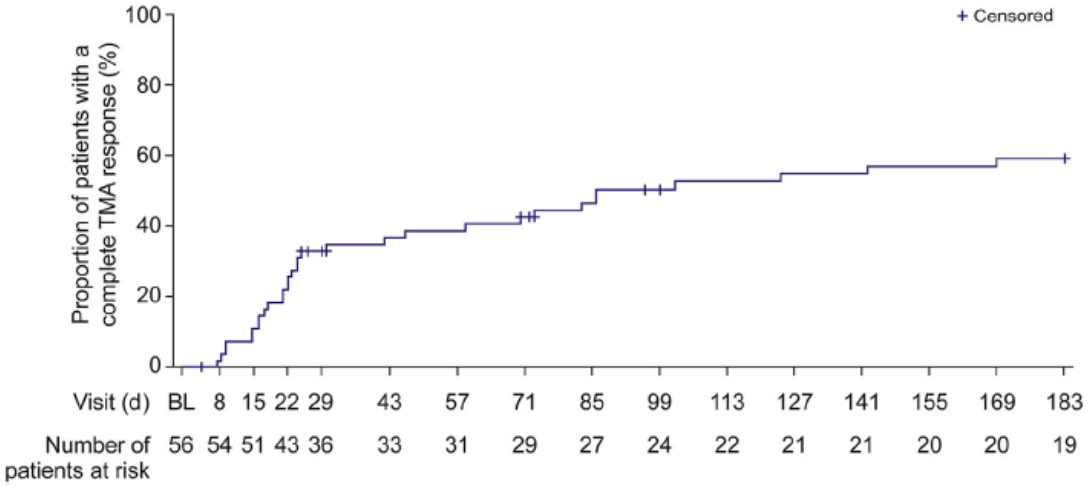
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], one additional patient initiated and discontinued dialysis within the Initial Evaluation Period; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [e], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.

Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]; EMA Variation Assessment Report[39]; Rondeau et al. 2020.[34]

B.2.6.1.1 ALXN1210-aHUS-311

Primary endpoint: ravulizumab treatment resulted in complete TMA response for 54% of patients during the Initial Evaluation Period (Table 8). Complete TMA response occurred as early as 7 days from the first ravulizumab infusion and was attained in a median time of 86 days; the number of patients with a complete TMA response continued to increase over time, as depicted in Figure 5.

Figure 5: Kaplan–Meier plot of time to complete TMA response in ALXN1210-aHUS-311: Initial Evaluation Period (FAS)



Key: BL, baseline; d, day; FAS, full analysis set; TMA, thrombotic microangiopathy.
Notes: Patients who did not have a response were censored on the day of their last study visit or at study discontinuation.
Source: Rondeau et al. 2020.[34]

Haematological endpoints: over two-thirds of patients (73%) achieved haematological normalization, with 84% of patients achieving platelet count normalization and 77% of patients achieving LDH normalization (Table 8). Platelet counts showed the earliest response, with [redacted] of patients achieving platelet count normalization by Day 15.[40]

A substantial increase in haemoglobin from baseline was observed (median increase: 35 g/L) with 71% of patients achieving an increase in haemoglobin of at least 20 g/L by the end of the Initial Evaluation Period (Table 8).

Observed laboratory values over time are presented graphically in Appendix L.

Renal endpoints: renal function improvement defined as ≥25% reduction in serum creatinine from baseline was observed in 59% of patients (Table 8). A substantial increase in the estimated glomerular filtration rate (eGFR) from baseline was observed by Day 15 with a median increase of 29 mL/min/1.73 m^2 by the end of the Initial Evaluation Period (Table 8).

Improvement in eGFR aligning to a CKD stage improvement was seen in 68% of patients with available data (Table 8). Two patients had a worsening in CKD stage: [redacted].[40] [redacted] Table 9 shows how patients moved between CKD stages during the Initial Evaluation Period.

Dialysis was discontinued in 59% of patients who were on dialysis at baseline by a median time of 30 days.[34] Of patients not on dialysis at baseline, 78% remained off dialysis at the last available follow-up evaluation (which may have occurred after Day 183).

Table 9: CKD stage shift from baseline in ALXN1210-aHUS-311: Initial Evaluation Period (FAS)

CKD stage	Baseline n (%)	CKD stage at Day 183					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	3 (6.4)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3A	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3B	2 (4.3)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	7 (14.9)	1 (2.1)	0 (0.0)	0 (0.0)	3 (6.4)	1 (2.1)	2 (4.3)
5	34 (72.3)	6 (12.8)	6 (12.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)
Total	47 (100.0)	12 (25.5)	7 (14.9)	3 (6.4)	6 (12.8)	6 (12.8)	13 (27.7)

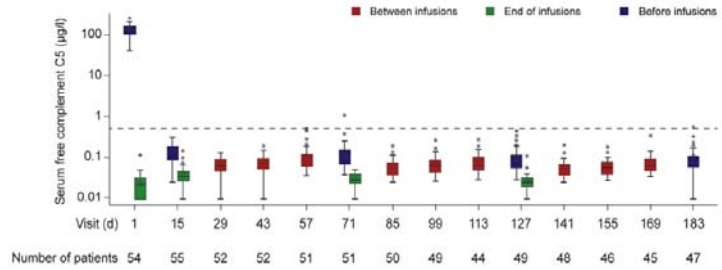
Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: Rondeau et al. 2020.[34]

Health-related quality of life (HRQL) endpoints: of patients with FACIT-Fatigue data at baseline and at the end of the Initial Evaluation Period (n=44), 84% reported a ≥3-point improvement in FACIT-Fatigue score (Table 8) that has previously been reported to represent clinically meaningful improvement in fatigue for adults.[42] At the end of the Initial Evaluation Period, the mean FACIT-Fatigue score was [redacted] compared with a baseline value of [redacted], representing very little fatigue across the study group (maximum score representing no fatigue is 52).[40]

Of patients with EQ-5D-3L data at baseline and at the end of the Initial Evaluation Period ([redacted]), a clinically meaningful improvement in HRQL was reported with a mean change in visual analogue scale (VAS) score of [redacted] and a mean change in time trade-off (TTO) of [redacted] (TTO value set for the US) (Table 8). At the end of the Initial Evaluation Period, the mean EQ-5D VAS score was [redacted] compared with a baseline value of [redacted], representing good quality of life on this 0-100 scale.[40]

Pharmacokinetic (PK)/pharmacodynamic (PD) endpoints: ravulizumab achieved immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) by the end of the first infusion and this was sustained throughout the Initial Evaluation Period, as depicted in Figure 6. No resistance in C5 was noted, with the majority of post-dose samples (852/856; 99.5%) having shown complete C5 inhibition.[34]

Figure 6: Serum free C5 concentration-time profile in ALXN1210-aHUS-311: Initial Evaluation Period (PK/PD analysis set)

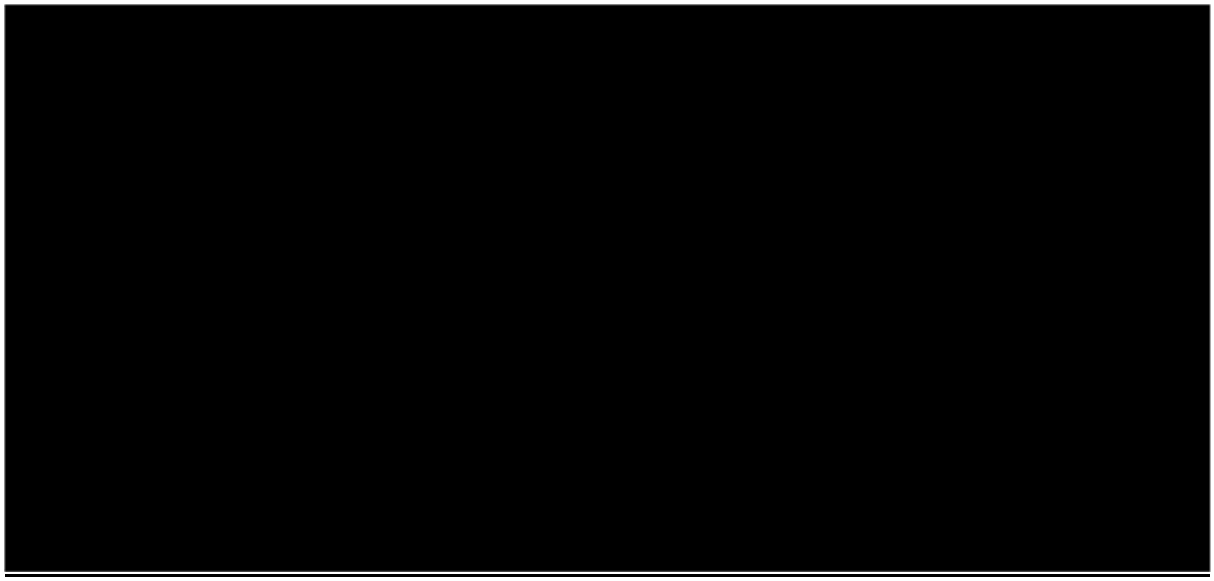


Key: d, day; PD, pharmacodynamic; PK, pharmacokinetic.
Notes: Horizontal line is drawn at free C5 at 0.5 ug/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 x the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.
Source: Rondeau et al. 2020.[34]

B.2.6.1.2 ALXN1210-aHUS-312 – Cohort 1

Primary endpoint: ravulizumab treatment resulted in complete TMA response for 78% of patients during the Initial Evaluation Period (Table 8). Complete TMA response occurred as early as [redacted] days from the first ravulizumab infusion and was attained in a median time of [redacted] days; the number of patients with a complete TMA response continued to increase over time, as depicted in Figure 7.

Figure 7: Kaplan–Meier plot of time to complete TMA response in ALXN1210-aHUS-312: Initial Evaluation Period + Extension Period up to Day 351 (FAS; Cohort 1)



Key: BL, baseline; CI, confidence interval; FAS, full analysis set; NO, number; TMA, thrombotic microangiopathy.
Notes: Patients who did not have a response were censored on the day of their last study visit or at study discontinuation.
Source: ALXN1210-aHUS-312 CSR.[41]

Haematological endpoints: the majority of patients (89%) achieved haematological normalization, with all but one patient achieving platelet count normalization and all but two patients achieving LDH normalization (Table 8). Platelet counts showed the earliest response, with [redacted] of patients achieving platelet count normalization by Day 15.[41]

A substantial increase in haemoglobin from baseline was observed (median increase: [redacted] g/L) with 89% of patients achieving an increase in haemoglobin of at least 20 g/L by the end of the Initial Evaluation Period (Table 8).

Renal endpoints: renal function improvement defined as ≥25% reduction in serum creatinine from baseline was observed in [redacted]% of patients (Table 8). A substantial increase in eGFR from baseline was observed by Day 15 with a median increase of [redacted] mL/min/1.73 m^2 by the end of the Initial Evaluation Period (Table 8).

Improvement in eGFR aligning to a CKD stage improvement was seen in [redacted]% of patients with available data and [redacted] had a worsening in CKD stage (Table 8). Table 10 shows how patients moved between CKD stages during the Initial Evaluation Period.

Table 10: CKD stage shift from baseline in ALXN1210-aHUS-312: Initial Evaluation Period (FAS; Cohort 1)

CKD stage	Baseline n (%)	CKD stage at Day 183					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: ALXN1210-aHUS-312 CSR.[41]

Dialysis was discontinued in [redacted]% of patients who were on dialysis at baseline within the first [redacted] days of ravulizumab exposure.[41] [redacted]

HRQL endpoints: of patients ≥5 years old with Paediatric FACIT-Fatigue data at baseline and at the end of the Initial Evaluation Period (n=9), [redacted]% reported a ≥3-point improvement in FACIT-Fatigue score (Table 8). At the end of the Initial Evaluation Period, the mean FACIT-Fatigue score was [redacted] compared with a mean baseline value of [redacted], representing very little fatigue across the study group.[41]

PK/PD endpoints: ravulizumab achieved immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) by the end of the first infusion and this was sustained throughout the Initial Evaluation Period, as depicted in Figure 8.

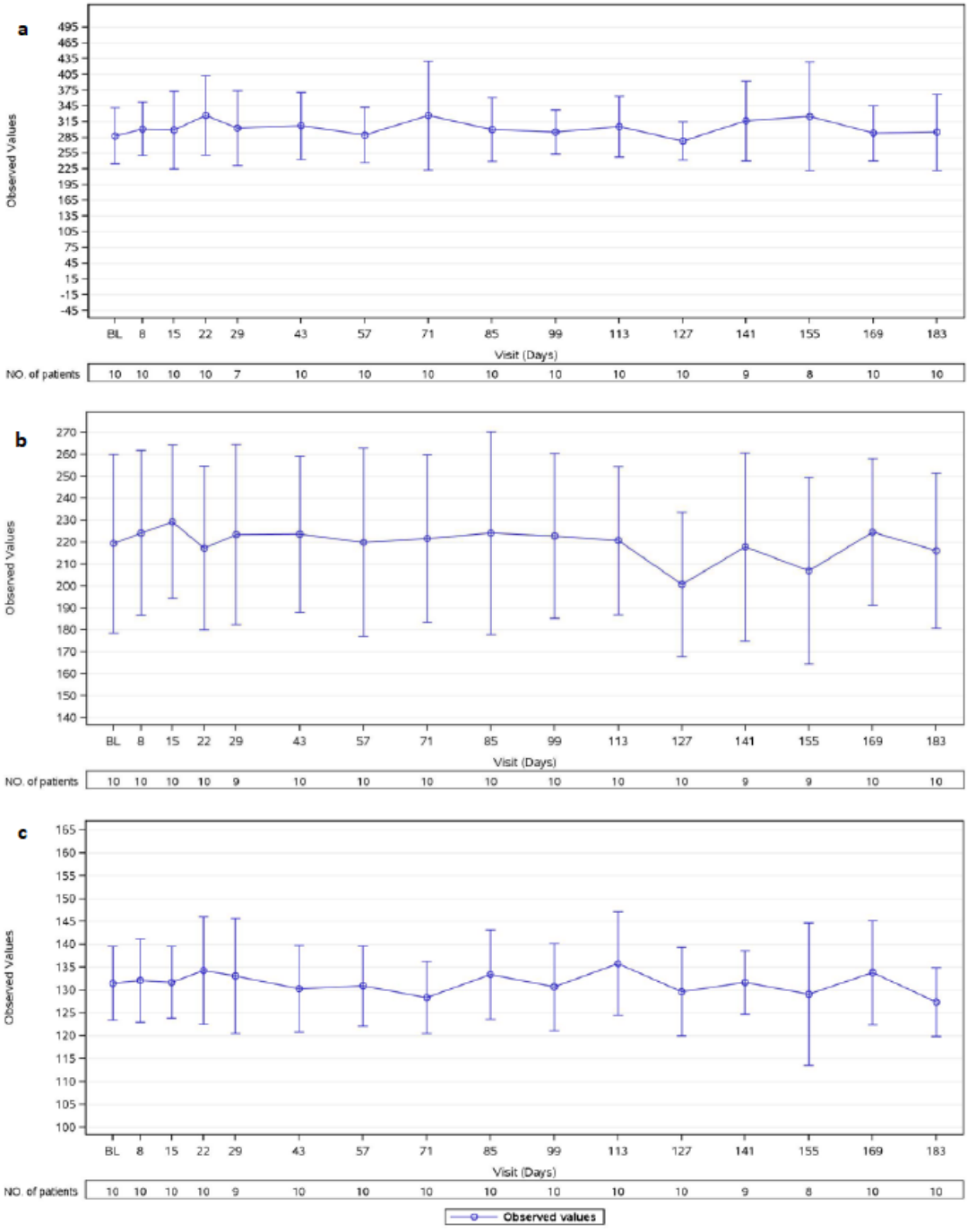
Figure 8: Serum free C5 concentration-time profile in ALXN1210-aHUS-312: Initial Evaluation Period (PK/PD analysis set; Cohort 1)

Key: PD, pharmacodynamic; PK, pharmacokinetic; NO, number.
Notes: Horizontal line is drawn at free C5 at 0.5 ug/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 x the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.
Source: ALXN1210-aHUS-312 CSR.[41]

B.2.6.1.3 ALXN1210-aHUS-312 – Cohort 2

Haematological endpoints: haematological parameters remained stable following the 'switch' from eculizumab to ravulizumab, as depicted in Figure 9.

Figure 9: **Observed laboratory values (a) platelet count (b) LDH (c) haemoglobin in ALXN1210-aHUS-312: Initial Evaluation Period (FAS; Cohort 2)**



Key: LDH, lactate dehydrogenase; FAS, full analysis set; NO, number.
Source: EMA Variation Assessment Report.[39]

Renal endpoints: renal function generally remained stable following the 'switch' from eculizumab to ravulizumab, although a [redacted], as shown in Table 11. [redacted] Table 15 [redacted] Table 15 [redacted] Individual eGFR charts for these patients are provided in Appendix F. [redacted] were initiated on dialysis while receiving ravulizumab.[41]

Table 11: CKD stage shift from baseline in ALXN1210-aHUS-312: Initial Evaluation Period (FAS; Cohort 2)

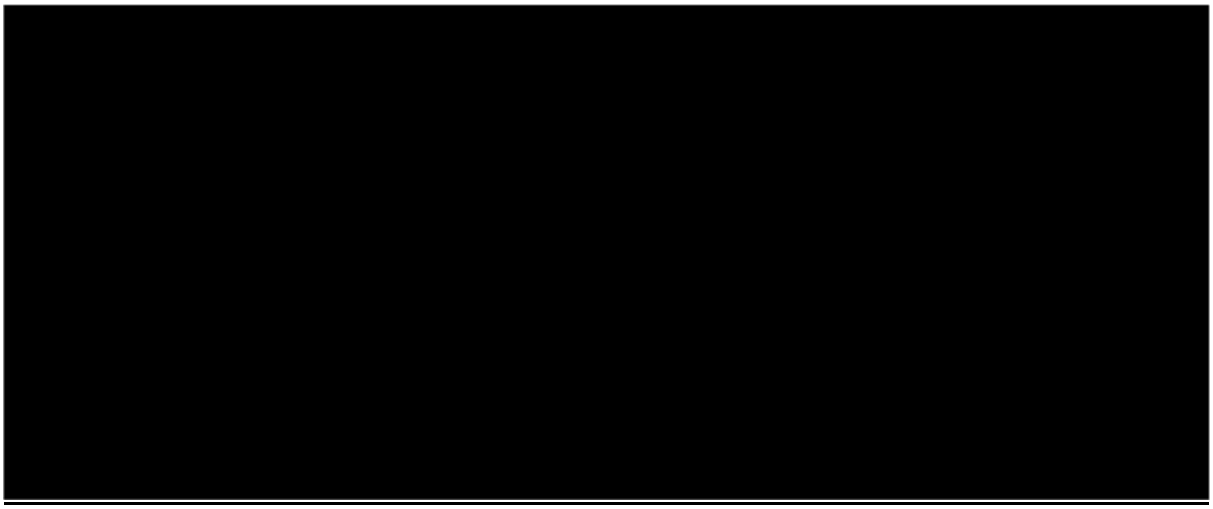
CKD stage	Baseline n (%)	CKD stage at Day 183					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: ALXN1210-aHUS-312 CSR.[41]

HRQL endpoints: HRQL remained stable following the 'switch' from eculizumab to ravulizumab, with no notable improvements or worsening in Paediatric FACIT-Fatigue scores for patients ≥5 years old ([redacted]).[41]

PK/PD endpoints: ravulizumab achieved immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) by the end of the first infusion and this was sustained throughout the Initial Evaluation Period, as depicted in Figure 10.

Figure 10: Serum free C5 concentration-time profile in ALXN1210-aHUS-312: Initial Evaluation Period (PK/PD analysis set; Cohort 2)



Key: PD, pharmacodynamic; PK, pharmacokinetic; NO, number.
Notes: Horizontal line is drawn at free C5 at 0.5 ug/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 x the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.
Source: ALXN1210-aHUS-312 CSR.[41]

B.2.6.2 Extension Period

Table 12 provides an overview of efficacy results as of data cut-off for the FAS population. Primary and secondary outcomes of interest to the decision problem are summarized in turn below.

Table 12: Summary of efficacy results from ALXN1210-aHUS-311 and ALXN1210-aHUS-312: Extension Period up to data cut-off (FAS)

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Complete TMA response, n (%) [95% CI]	[redacted]	[redacted]	Not relevant
Platelet count normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]
Change in platelet count, Median x 10^9/L (range)	Day 407 [redacted]	Day 407 [redacted]	Day 351 [redacted]
LDH normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]
Change in LDH, Median U/L (range)	Day 407 [redacted]	Day 407 [redacted]	Day 351 [redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	[redacted]	[redacted]	Not relevant
Haematologic normalization[a], n (%) [95% CI]	[redacted]	[redacted]	Not relevant
Haemoglobin response[b], n (%) [95% CI]	[redacted]	[redacted]	[redacted]
Change in haemoglobin, Median g/L (range)	Day 407 [redacted]	Day 407 [redacted]	Day 351 [redacted]
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	Day 407 [redacted]	Day 407 [redacted]	Day 351 [redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	Day 407 [redacted]	Day 407 [redacted]	Day 351 [redacted]
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline[c], n/N (%)	[redacted]	[redacted]	Not relevant [redacted]
CKD stage improvement, n/N (%)	[redacted]	[redacted]	[redacted]
CKD stage worsening, n/N (%)	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	Day 351 [redacted]	Day 351 [redacted]	Day 351 [redacted]

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	Day 351 [redacted]	Day 351 [redacted]	Not relevant
Change in EQ-5D-3L score, Mean VAS (SD) (n=41) Mean TTO[e] (SD) (n=42)	Day 351 [redacted] [redacted]	Not collected	Not collected

Key: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], data presented across the initial evaluation and extension periods; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. Day 351 data reported as patient numbers markedly drop off after this point; [e], TTO value set for the US.
Data are presented up to data cut-off unless otherwise stated.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]

B.2.6.2.1 ALXN1210-aHUS-311

The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks).[40]

Primary endpoint: [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off (2 July 2019) (Table 12). The latest complete TMA response was observed at [redacted].[40]

Haematological endpoints: [redacted] to those who achieved platelet count and LDH normalization in the Initial Evaluation Period reached this goal in the Extension Period, respectively (Table 12). An additional [redacted] patients achieved a haemoglobin response, bringing the total to [redacted]% (Table 12).

Renal endpoints: renal function improvement observed in the Initial Evaluation Period was maintained in the Extension Period with a median eGFR at Day 407 of [redacted] mL/min/1.73 m^2 (Table 12). Dialysis was discontinued in [redacted] of those who were on dialysis at baseline. [redacted]

[redacted].[40] In UK practice, these patients would likely be classed as 'late presenters' with little expectation of a response to complement-inhibitor treatment. Tabulation of how patients moved between CKD stages from baseline to Day 407 is provided in Table 13.

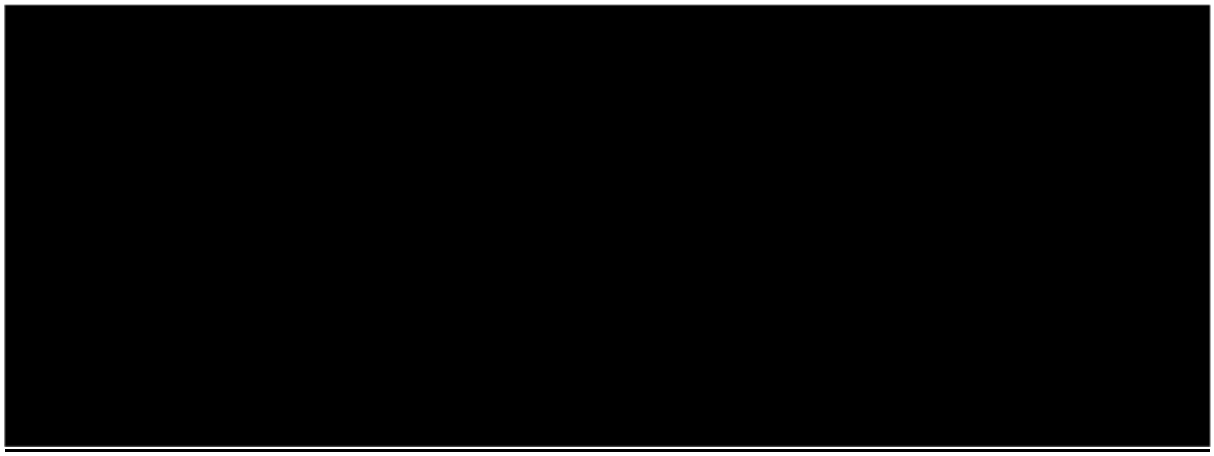
Table 13: CKD stage shift from baseline in ALXN1210-aHUS-311: Extension Period up to Day 407 (FAS)

CKD stage	Baseline n (%)	CKD stage at Day 407					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: Rondeau et al. 2020.[34]

HRQL endpoints: HRQL, as measured by FACIT-Fatigue, remained stable throughout the extension period, as depicted in Figure 11. At Day 351, the mean FACIT-Fatigue score was [redacted] compared with a mean baseline value of [redacted], representing very little fatigue in patients following ravulizumab treatment.[40] The same was observed with EQ-5D data, with a Day 351 mean EQ-5D VAS of [redacted] compared with a baseline value of [redacted] (0-100 scale).[40]

Figure 11: Observed FACIT-Fatigue score in ALXN1210-aHUS-311 from baseline: Extension Period up to Day 575 (FAS)



Key: FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set.
Notes: Mean scores are displayed with error bars representing standard deviation. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue.
Source: adapted from ALXN1210-aHUS-311 CSR.[40]

PK/PD endpoints: ravulizumab continued to provide immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) across an 8-week dosing interval in the Extension Period.

B.2.6.2.2 ALXN1210-aHUS-312 – Cohort 1

The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks).[41]

Primary endpoint: [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off (3 December 2019) (Table 12). The latest complete TMA response was observed at [redacted].[41]

Haematological endpoints: [redacted] to those who achieved (i) LDH normalization and (ii) haemoglobin response in the Initial Evaluation Period reached this goal in the Extension Period (Table 12).

Renal endpoints: renal function improvement observed in the Initial Evaluation Period was maintained in the Extension Period with a median eGFR at Day 407 of

[redacted]mL/min/1.73 m^2 (Table 12). The [redacted] who entered the study on dialysis were able to discontinue dialysis in the Extension Period and [redacted] who were not on dialysis at baseline remained off dialysis (Table 12). Likewise, for patients with available data at baseline and on Day 407, [redacted] an improvement in CKD stage. Tabulation of how patients moved between CKD stages from baseline to Day 407 is provided in Table 14.

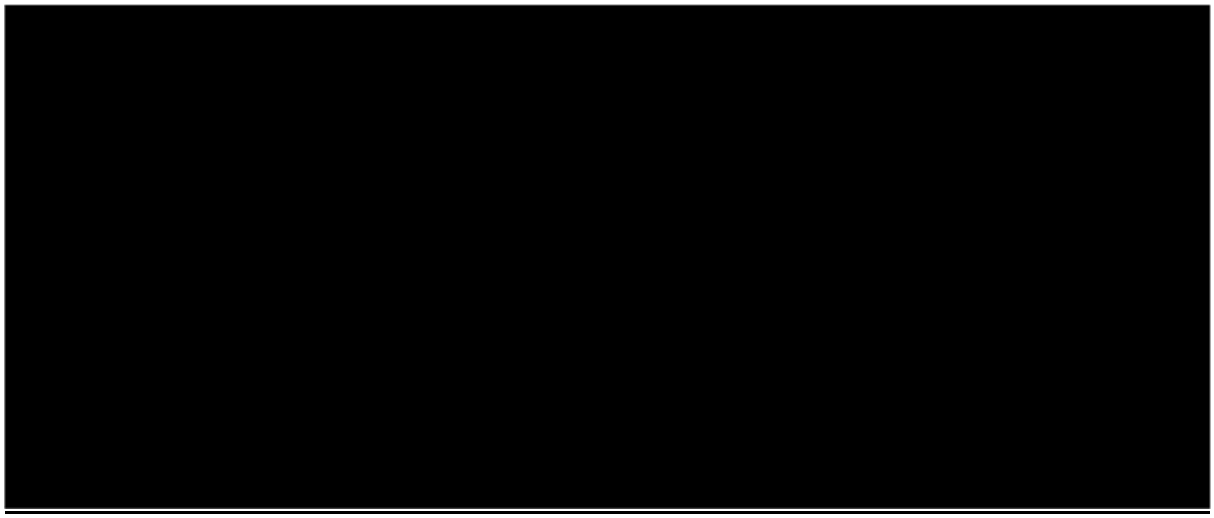
Table 14: CKD stage shift from baseline in ALXN1210-aHUS-312: Extension Period up to Day 407 (FAS; Cohort 1)

CKD stage	Baseline n (%)	CKD stage at Day 407					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: ALXN1210-aHUS-312 CSR.[41]

HRQL endpoints: HRQL, as measured by Paediatric FACIT-Fatigue score, remained stable throughout the extension period, as depicted in Figure 12. At Day 351, the mean FACIT-Fatigue score was [redacted] compared with a mean baseline value of [redacted], representing very little fatigue in patients following ravulizumab treatment.[41]

Figure 12: Observed Paediatric FACIT-Fatigue score in ALXN1210-aHUS-312 from baseline: Extension Period up to Day 575 (FAS; Cohort 1)



Key: BL, baseline; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set.
Notes: Mean scores are displayed with error bars representing 95% confidence intervals. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue.
Source: ALXN1210-aHUS-312 CSR.[41]

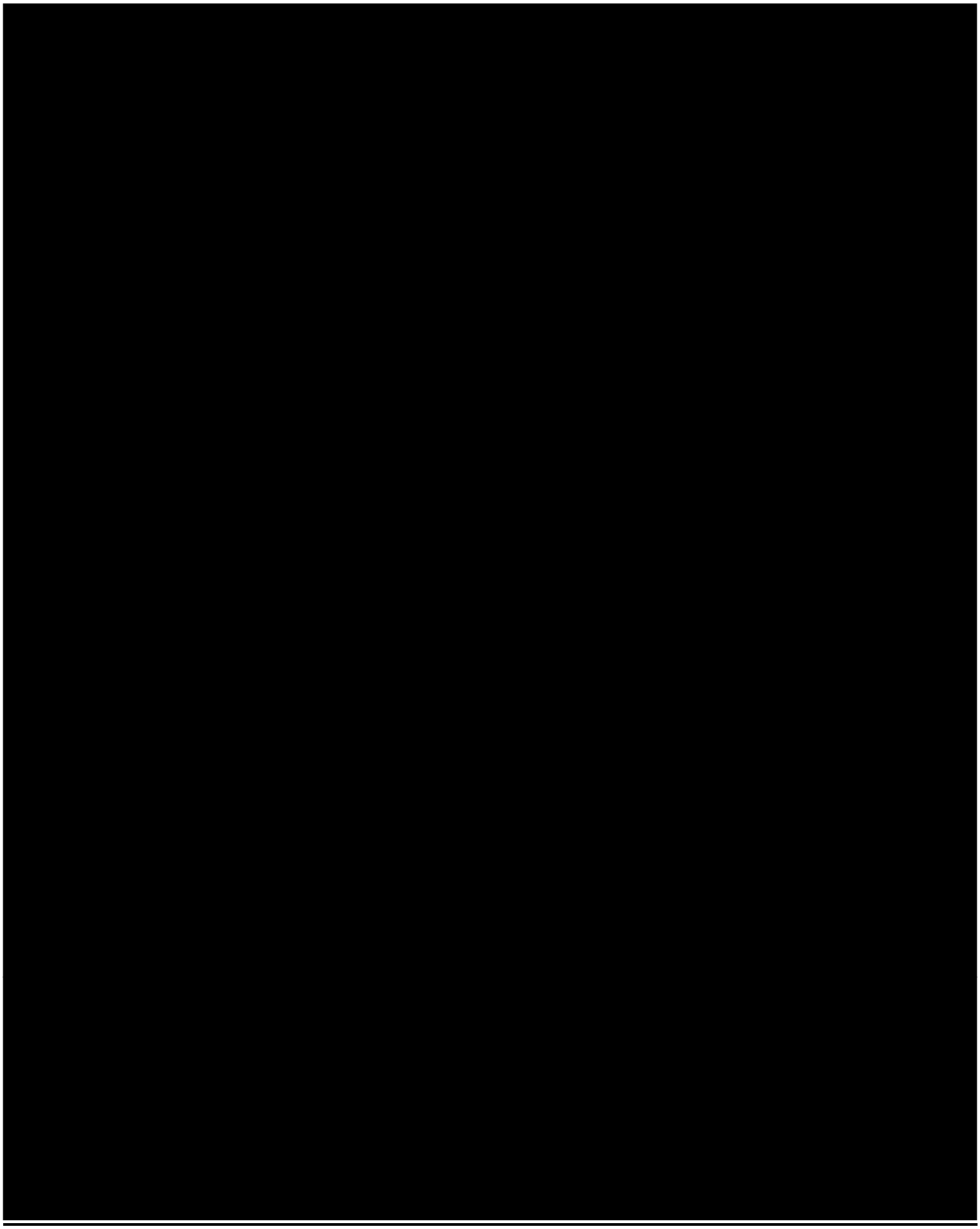
PK/PD endpoints: ravulizumab continued to provide immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) across an 8-week dosing interval in the Extension Period.

B.2.6.2.3 ALXN1210-aHUS-312 – Cohort 2

The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks).[41]

Haematological endpoints: haematological parameters remained stable throughout the Extension Period, as depicted in Figure 13.

Figure 13: Observed laboratory values (a) platelet count (b) LDH (c) haemoglobin in ALXN1210-aHUS-312: Extension Period up to Day 407 (FAS; Cohort 2)



Key: LDH, lactate dehydrogenase; FAS, full analysis set; NO, number.
Source: ALXN1210-aHUS-312 CSR.[41]

Renal endpoints: renal function remained stable throughout the Extension Period with a median eGFR at Day 407 of [redacted] mL/min/1.73 m^2 (Table 12). [redacted] remain off dialysis and [redacted].[41]

Tabulation of how patients moved between CKD stages from baseline to Day 351 is provided in Table 15.

Table 15: CKD stage shift from baseline in ALXN1210-aHUS-312: Extension Period up to Day 351 (FAS; Cohort 2)

CKD stage	Baseline n (%)	CKD stage at Day 351					
		1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Notes: Green text indicates improvement compared to baseline and red text indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Source: ALXN1210-aHUS-312 CSR.[41]

HRQL endpoints: HRQL remained stable throughout the Extension Period, with no significant change in Paediatric FACIT-Fatigue score from baseline at the Day 351 visit (median change: [redacted]) (Table 12).

PK/PD endpoints: ravulizumab continued to provide immediate, complete and sustained terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) across an 8-week dosing interval in the Extension Period.

B.2.7. Subgroup analysis

Subgroup analysis was conducted for the primary endpoint based on sex, race, ethnicity, geographic region, age, kidney transplant history, immunogenicity status and dialysis status at baseline in both trials. A further subgroup based on TMA status at baseline was also explored in ALXN1210-aHUS-311.

The complete TMA response rate was generally consistent across subgroups in ALXN1210-aHUS-311 compared with the overall population, although lower rates were noted among patients with a history of kidney transplant and Asian patients. Non-responders were predominantly at the older end of the age distribution and mostly at CKD stage 5.

Although not a prespecified subgroup, it was also noted in the ALXN1210-aHUS-311 trial that [redacted] patients who had onset of TMA post-partum achieved complete TMA response by Day 43.[40]

Subgroup analysis was limited to Cohort 1 patients in ALXN1210-aHUS-312 but the number of patients contributing to the data were very small and the results are not considered meaningful in consideration of these low patient numbers.

Forest plots of subgroup analysis are provided in Appendix E.

B.2.8. Meta-analysis

Meta-analysis is not appropriate as the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trials provide data for distinct populations: adult and paediatric patients, respectively.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1 Introduction to the indirect treatment comparisons

In the absence of head-to-head data, estimates of the comparative benefits of ravulizumab compared with eculizumab are provided through ITC. Full details of the methodology for the ITC are provided in Appendix D. In summary, patient-level data from ravulizumab trials (described in previous sections of this submission) and pivotal eculizumab trials (described in Appendix D) were pooled into a single dataset

and propensity scoring used to balance groups across treatment arms based on observed patient characteristics. Table 16 summarizes these trials.

Table 16: Summary of trials and populations used to carry out the indirect treatment comparison

Trial ID	Study design	Population	Intervention
ALXN1210-aHUS-311[34] NCT02949128	Phase III Single group assignment Open-label Multinational	Adults with aHUS who are complement inhibitor treatment-naïve (n=58)	Ravulizumab
ALXN1210-aHUS-312[41] NCT03131219	Phase III Single group assignment Open-label Multinational	Children and adolescents with aHUS who are complement inhibitor treatment-naïve (n=21)[a]	Ravulizumab
aHUS-C08-002[30] NCT00844545 NCT00844844	Phase II Single group assignment Open-label Multinational	People with aHUS who are complement inhibitor treatment-naïve and plasma therapy-resistant: • adults (n=16) • adolescents (n=1)	Eculizumab
aHUS-C10-003[29] NCT01193348	Phase II Single group assignment Open-label Multinational	Paediatric patients with aHUS who are complement inhibitor treatment-naïve (n=22)	Eculizumab
aHUS-C10-004[28] NCT01194973	Phase II Single group assignment Open-label Multinational	Adults with aHUS who are complement inhibitor treatment-naïve (n=44)	Eculizumab

Key: aHUS, atypical haemolytic uremic syndrome.
Note: [a], Cohort 2 (patients clinically stable following ≥90 days treatment with eculizumab) not considered within the ITC as there are no comparable data for eculizumab.

Analyses were conducted on three populations:

- Adult patients, non-transplant
- Adult patients, transplant
- Paediatric patients, non-transplant

Adult and paediatric populations, and non-transplant and transplant populations were analysed separately as differences were seen in the absolute effect of complement-

inhibitor treatments across outcomes. Although the 'paediatric patients, transplant' population was considered for additional analyses, small patient numbers prevented this (see Figure 14).

Where there were differences in baseline definitions or outcome definitions, these were standardized prior to analyses. The definitions used in the pivotal ravulizumab trials provided the baseline for standardization. Data collected at 26-weeks were used to populate the analyses, aligning to the primary endpoints of all included trials.

Extensive clinical input was sought to inform the important characteristics to balance across treatment arms (that is, the variables used within the propensity score specification). In hierarchical order of importance, the characteristics considered important were:

- Dialysis status at baseline
- eGFR at baseline
- Platelet count at baseline
- LDH at baseline
- Systolic blood pressure at baseline

Because of similar systolic blood pressure at baseline values across treatment arms, this characteristic was not included in the propensity score formula. All other characteristics considered important were included. In the base case analysis, 'stabilized weights' were used to produce balanced groups[43]; when applying the stabilized weights, differences in characteristics included that were significant at the $p<0.1$ level were deemed sufficient to refactor the propensity score model.

All analysis was performed using the statistical software R version 3.6.3.

B.2.9.2 Results of the indirect treatment comparison

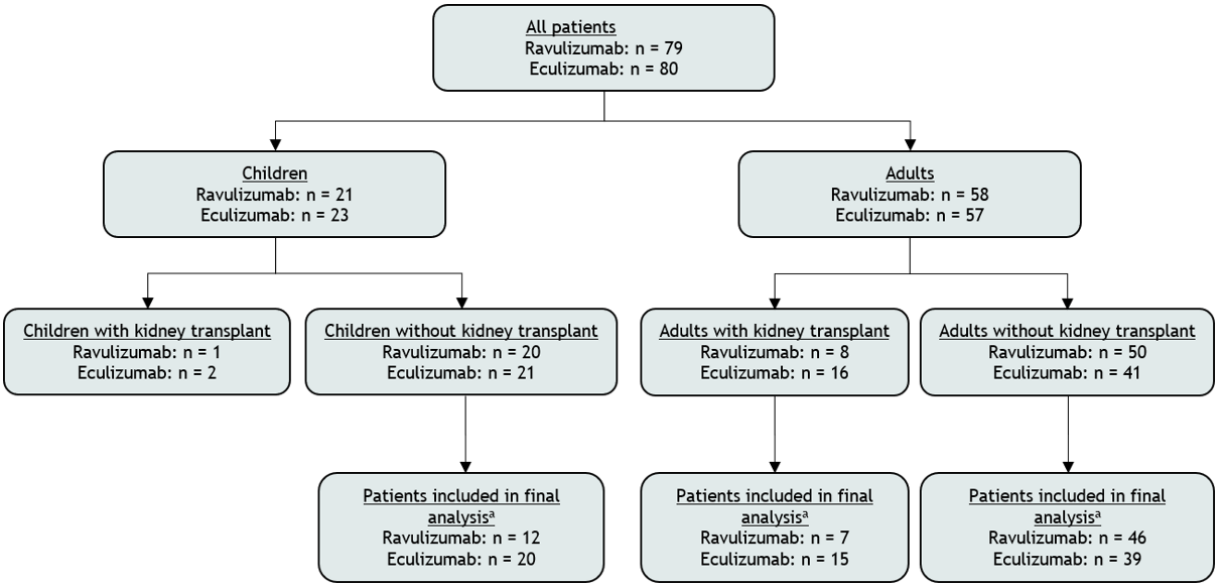
Figure 14 summarizes data availability for the populations considered for analyses. The number of patients from each trial that made up these populations are detailed in Appendix D; as are patient numbers for sensitivity analyses.

To be included in the final (base case) analysis, patients had to have:

- Complete data for the variables used within the propensity score specification
- No more than one missing laboratory variable at either baseline or endpoint
- Outcome data within 56 days of the 6-month study endpoint

The application of these restrictions reduced the patient numbers, as detailed in Figure 14. Death was considered as an outcome, and thus patients who died were included in the main analysis, regardless of the absence of endpoint laboratory values. A sensitivity analysis was performed excluding patients who died (n=3), as death may be seen as a non-treatment related random event.

Figure 14: Data availability for the populations considered for analyses



Note: [a], patients included in final analyses were those meeting the criteria described above.

Results of the base case analyses for the three populations considered are presented in this section, as well as sensitivity analyses of the 'adult patients, non-transplant' population that excluded patients who died in the study period. This sensitivity analyses is used to reflect adult, non-transplant patients in the subsequent economic scenario analysis (see Section B.3.3). Further sensitivity analyses are

provided in Appendix D. Propensity score specification results are also provided in Appendix D.

B.2.9.2.1 Baseline characteristics

Table 17 summarizes the baseline characteristics of patients before and after stabilized weights for the 'adult patients, non-transplant' population and Table 18 summarizes the same data excluding patients who died in the study period. The application of stabilized weights did not change the effective sample size calculated as the sum of weights in each treatment arm.

Prior to weighting, of those characteristics considered important, imbalances were observed in LDH levels at baseline, which were higher in the ravulizumab treatment arm (suggestive of more severe haemolysis). Patients also appeared older in the ravulizumab treatment arm and there was a higher proportion of Asian patients enrolled to the pivotal ravulizumab trials. After the application of stabilized weights, there were no clear imbalances between treatment arms in important characteristics; however, age and region differences remained (Table 17; Table 18)

Table 19 summarizes the baseline characteristics of patients before and after stabilized weights for the 'paediatric patients, non-transplant' population. The application of stabilized weights resulted in minor changes to the effective sample size calculated as the sum of weights in each treatment arm.

Prior to weighting, of those characteristics considered important, imbalances were observed in platelet count, eGFR for non-dialysis patients and systolic blood pressure at baseline, which were all lower in the ravulizumab arm (suggestive of more severe presentation). There was also a higher proportion of Asian patients enrolled to the pivotal ravulizumab trials. After the application of stabilized weights, there were no clear imbalances between treatment arms in important characteristics, however, region differences remained (Table 19).

Table 20 summarizes the baseline characteristics of patients before and after stabilized weights for the 'adult patients, transplant' population. The application of stabilized weights resulted in minor changes to the effective sample size calculated as the sum of weights in each treatment arm.

Prior to weighting, of those characteristics considered important, imbalances were observed in LDH levels at baseline, which was higher in the ravulizumab treatment arm (suggestive of more severe haemolysis); and in eGFR at baseline, which was lower in the ravulizumab arm (suggestive of more severe presentation). There was also a higher proportion of Asian patients enrolled to the pivotal ravulizumab trials. After the application of stabilized weights, there was an imbalance in systolic blood pressure, which was higher in the eculizumab treatment arm (suggestive of higher cardiac risk); there was also a higher proportion of males in the ravulizumab arm and region differences remained (Table 20).

Further detail on baseline characteristics before and after stabilized weight application for all populations is provided in Appendix D.

Table 17: Summary of baseline characteristics of patients before and after stabilized weights application: adult patients, non-transplant

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=46)[a]	Eculizumab (n=39)[a]	p-value (95% CI)[b]	Ravulizumab (ESS=46)[a]	Eculizumab (ESS=39)[a]	p-value (95% CI)[b]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%) Asia Ex-Asia	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
CKD stage, n (%) 1 2 3.1 3.2 4 5	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] 	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted]
Dialysis at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years Mean (SD) Median (range)	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
Age ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=46)[a]	**Eculizumab (n=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=46)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH, U/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure, mmHg Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SD, standard deviation.
Notes: [a], unless otherwise stated; [b], represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at baseline).

Table 18: Summary of baseline characteristics of patients before and after stabilized weights application: adult patients, non-transplant excluding patients who died in the study period

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=43)[a]	Eculizumab (n=39)[a]	p-value (95% CI)[b]	Ravulizumab (ESS=43)[a]	Eculizumab (ESS=39)[a]	p-value (95% CI)[b]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%) Asia Ex-Asia	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
CKD stage, n (%) 1 2 3.1 3.2 4 5	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]		 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	
Dialysis at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years Mean (SD) Median (range)	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
Age ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=43)[a]	**Eculizumab (n=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=43)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH, U/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure, mmHg Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SD, standard deviation.
Notes: [a], unless otherwise stated; [b], represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at baseline).

Table 19: Summary of baseline characteristics of patients before and after stabilized weights application: paediatric patients, non-transplant

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=12)[a]	Eculizumab (n=20)[a]	p-value (95% CI)[b]	Ravulizumab (ESS=10.7)[a]	Eculizumab (ESS=21.3)[a]	p-value (95% CI)[b]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%) Asia Ex-Asia	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
CKD stage, n (%) 1 2 3.1 3.2 4 5	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] 	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted]
Dialysis at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years Mean (SD) Median (range)	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
Age ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=12)[a]	**Eculizumab (n=20)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH, U/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure, mmHg Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SD, standard deviation.
Notes: [a], unless otherwise stated; [b], represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at baseline).

Table 20: Summary of baseline characteristics of patients before and after stabilized weights application: adult patients, transplant

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=7)[a]	Eculizumab (n=15)[a]	p-value (95% CI)[b]	Ravulizumab (ESS=9.3)[a]	Eculizumab (ESS=12.7)[a]	p-value (95% CI)[b]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%) Asia Ex-Asia	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	
CKD stage, n (%) 1 2 3.1 3.2 4 5	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] 	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted]
Dialysis at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years Mean (SD) Median (range)	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]
Age ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Prior to weighting			After the application of stabilized weights		
	Ravulizumab (n=7)[a]	**Eculizumab (n=15)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=9.3)[a]**	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH, U/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure, mmHg Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SD, standard deviation.
Notes: [a], unless otherwise stated; [b], represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at baseline).

B.2.9.2.2 Outcomes

Table 21 summarizes outcomes of patients after stabilized weights for the 'adult patients, non-transplant' population (base case and sensitivity analyses excluding patients who died in the study period).

As expected, there were no statistically significant differences observed between treatment groups for any outcomes after stabilized weights were applied in the base case analyses or the sensitivity analyses. Both ravulizumab and eculizumab were associated with substantial improvements in renal function, haematological markers and HRQL. There were some numerical differences observed but these did not represent consistent trends in favour of one treatment or the other. For example, although a higher proportion of patients appeared to come off dialysis with eculizumab, eGFR improved more with ravulizumab, and while mean LDH values were lower after eculizumab treatment, the reduction in LDH from baseline was greater with ravulizumab treatment. There was a difference in the number of deaths between treatment arms; this is discussed in Section B.2.10.3 but in summary, is not considered related to treatment. Sensitivity analyses that excluded patients who died in the study period supported the base case analyses (Table 21), advocating the use of these sensitivity analyses in the subsequent economic scenario analysis.

Table 22 summarizes outcomes of patients after stabilized weights for the 'adult patients, transplant' population and for the 'paediatric patients, non-transplant' population.

Again, as expected, there were no statistically significant differences observed between treatment groups for any outcomes after stabilized weights were applied in these populations. Both ravulizumab and eculizumab were associated with substantial improvements in renal function, haematological markers and HRQL. Again, there were some numerical differences observed but these did not represent consistent trends in favour of one treatment or the other. There was one death in the ravulizumab arm of the 'adult patients, transplant' population (not related to treatment) that is discussed in Section B.2.10.3.

Table 21: Outcomes of patients after stabilized weights application: adult patients, non-transplant base case analysis and sensitivity analysis that excluded patients who died

	Adult patients, non-transplant			Adult patients, non-transplant, excluding patients who died		
	Ravulizumab (ESS=46)[a]	Eculizumab (ESS=39)[a]	p-value (95% CI)[b]	Ravulizumab (ESS=43)[a]	Eculizumab (ESS=39)[a]	p-value (95% CI)[b]
cTMA response, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to cTMA response, days Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis at endpoint, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died in trial, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage, n (%) [95% CI] 0 1 2 3A 3B 4 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, non-transplant			Adult patients, non-transplant, excluding patients who died		
	Ravulizumab (ESS=46)[a]	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=43)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
Change in CKD stage, n (%) [95% CI] Improved Unchanged Worsened	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Creatine in non-dialysis patients, µmol/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in creatinine in non-dialysis patients Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in creatinine in non-dialysis patients, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in platelet count Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, non-transplant			Adult patients, non-transplant, excluding patients who died		
	Ravulizumab (ESS=46)[a]	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=43)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
LDH, U/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in LDH Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematologic normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]			
eGFR, mL/min/1.73 m^2 Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in eGFR Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in eGFR, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR for non-dialysis patients Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, non-transplant			Adult patients, non-transplant, excluding patients who died		
	Ravulizumab (ESS=46)[a]	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=43)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
CFB in eGFR for non-dialysis patients Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in eGFR for non-dialysis patients, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure, mmHg Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in systolic blood pressure Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT subscale score Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in FACIT subscale score Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3-point improvement in FACIT subscale score, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS score Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, non-transplant			Adult patients, non-transplant, excluding patients who died		
	Ravulizumab (ESS=46)[a]	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=43)[a]**	**Eculizumab (ESS=39)[a]**	**p-value (95% CI)[b]**
CFB in EQ-5D VAS score Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10-point improvement in EQ-5D VAS score, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D TTO score[c] Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in EQ-5D TTO score[c] Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BMI, Body Mass Index; CFB, change from baseline; CI, confidence interval; CKD, chronic kidney disease; LDH, lactate dehydrogenase; eGFR, estimated Glomerular Filtration Rate; EQ-5D, EuroQol-5 Dimension; FACIT, Functional Assessment of Chronic Illness Therapy; SD, standard deviation; TTO, time trade-off; VAS, visual analogue scale.

Notes: [a], unless otherwise stated; [b], 95% CIs represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at end point). Percentages may not sum to 100% due to rounding; [c], TTO value set for the US.

Table 22: Outcomes of patients after stabilized weights application: adult patients, transplant and paediatric patients, non-transplant

	Adult patients, transplant			Paediatric patients, non-transplant		
	Ravulizumab (ESS=9.3)[a]	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
cTMA response, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to cTMA response, days Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis at endpoint, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died in trial, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage, n (%) [95% CI] 0 1 2 3A 3B 4 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, transplant			Paediatric patients, non-transplant		
	Ravulizumab (ESS=9.3)[a]	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
Change in CKD stage, n (%) [95% CI] Improved Unchanged Worsened	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Creatine in non-dialysis patients, µmol/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in creatinine in non-dialysis patients Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in creatinine in non-dialysis patients, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count x 10^9/L Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in platelet count Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count normalization, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, transplant			Paediatric patients, non-transplant		
	Ravulizumab (ESS=9.3)[a]	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
LDH, U/L	[redacted]	[redacted]				[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in LDH	[redacted]	[redacted]	[redacted]			[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH normalization, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematologic normalization, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mL/min/1.73 m^2	[redacted]	[redacted]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in eGFR	[redacted]	[redacted]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in eGFR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR for non-dialysis patients	[redacted]	[redacted]		[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in eGFR for non-dialysis patients	[redacted]	[redacted]		[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Adult patients, transplant			Paediatric patients, non-transplant		
	Ravulizumab (ESS=9.3)[a]	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
Improvement in eGFR for non-dialysis patients, n (%) [95% CI]						
Systolic blood pressure, mmHg Mean (SD) Median (range)						
CFB in systolic blood pressure Mean (SD) Median (range)						
FACIT subscale score Mean (SD) Median (range)						
CFB in FACIT subscale score Mean (SD) Median (range)						
≥4.7-point improvement in FACIT subscale score[c], n (%) [95% CI]						
≥3-point improvement in FACIT subscale score, n (%) [95% CI]						
EQ-5D VAS score Mean (SD) Median (range)						
CFB in EQ-5D VAS score Mean (SD) Median (range)						

	Adult patients, transplant			Paediatric patients, non-transplant		
	Ravulizumab (ESS=9.3)[a]	**Eculizumab (ESS=12.7)[a]**	**p-value (95% CI)[b]**	**Ravulizumab (ESS=10.7)[a]**	**Eculizumab (ESS=21.3)[a]**	**p-value (95% CI)[b]**
≥10-point improvement in EQ-5D VAS score, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D TTO score[d] Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in EQ-5D TTO score[d] Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BMI, Body Mass Index; CFB, change from baseline; CI, confidence interval; CKD, chronic kidney disease; LDH, lactate dehydrogenase; eGFR, estimated Glomerular Filtration Rate; FACIT, Functional Assessment of Chronic Illness Therapy; SD, standard deviation.
Notes: [a], unless otherwise stated; [b], 95% CIs represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes and refer to the 95% CI around the difference between treatments for the first listed category (i.e. 'Yes' for dialysis at end point). Percentages may not sum to 100% due to rounding; [c], 4.7-point improvement used to represent a clinically meaningful improvement in the paediatric population; [d], TTO value set for the US.

B.2.9.3 Uncertainties in the indirect treatment comparison

The analyses performed represent best practice in using statistical methods to account for differences between populations and allow an unbiased cross-study comparison in the absence of head-to-head data. In general, the pooled datasets appeared well matched for patient characteristics, which is unsurprising given they were built from patient-level data taken from Alexion sponsored clinical studies in the same patient population. However, there were some notable differences that the propensity scoring addressed to give a more comparable dataset. In terms of method selection, the use of stabilized weights was preferred to maintain sample size, but also as it provided the best match across groups.

Assessment of outcomes after application of stabilized weights demonstrated that ravulizumab and eculizumab both result in substantial improvement in clinically relevant outcomes across adult and paediatric patients with aHUS. This included improvements in renal function, haematological markers and HRQL and was observed across base case and sensitivity analyses. As expected, there were no statistically significant differences observed between treatment groups for any outcomes, and although some numerical differences were observed, these did not represent consistent trends in favour of one treatment or the other. As such, we cannot conclude there are any clinically relevant differences between treatments based on the evidence available. One difference that should be acknowledged is in the number of deaths with three deaths in the ravulizumab arm compared to no deaths in the eculizumab arm in the ‘adult patients, non-transplant’ population analysis. This is discussed in Section B.2.10.3 but in summary, is not considered related to treatment.

While the availability of patient-level data allowed for standardization of baseline and outcome definitions in the majority, complete alignment for dialysis criteria was not possible. In the ravulizumab trials, a dialysis patient was defined as a patient who received dialysis within 5 days of the baseline/endpoint measure. The closest data available in the eculizumab patient-level data was dialysis within 7 days of the baseline/endpoint measure. Although this is a small difference, it could potentially impact results.

The main limitation of propensity scoring is that it provides an unbiased estimate conditional only on the observed characteristics. Should there be unobserved characteristics of importance, the effect of these on outcomes will not be accounted for. As patient-level data were available for both comparators of interest in this ITC, baseline characteristics were sufficiently captured, although some factors such as known pathogenic variant or autoantibody and use of plasma therapy were not consistently captured across studies and therefore could not be accounted for. There is also a ten-year gap in the trial programmes, over which time there are likely to have been changes in clinical care practice and general health and wellbeing that cannot be accounted for. A key difference observed in the baseline characteristics of patients across treatment arms was the high proportion of Asian patients enrolled to the pivotal ravulizumab trials. This was the result of Asian centres being included in the ravulizumab clinical trial programme, but not being included in the eculizumab clinical trial programme. A sensitivity analysis was conducted that excluded Asian patients with no impact on the overarching conclusion of the ITC, although outcomes were improved in the ravulizumab arm with the removal of Asian patients.

A further limitation of this analysis is the low number of patients, particularly in the ‘adult patients, transplant’ population and ‘paediatric patients, non-transplant’ populations. This is unavoidable in the context of an ultra-rare disease such as aHUS but does put a limit on the number of characteristics that could be included in the propensity score approach and increases the uncertainty around the result.

In conclusion, no statistically significant or clinically relevant differences were observed between ravulizumab and eculizumab, supporting an inference of equivalence between these complement-inhibitor treatments. A conclusion of equivalence is further supported by biological rationale, head-to-head data from the PNH setting, and the clinical community (see Section B.2.13).

B.2.10. Adverse reactions

B.2.10.1 Treatment exposure data

Table 23 provides treatment exposure data as of data cut-off for ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

In the Initial Evaluation Period, the median treatment duration in both studies (and both cohorts in the case of ALXN1210-aHUS-312) was [redacted] weeks.[40, 41] In the Extension Period, the median treatment duration ranged from [redacted] weeks (Table 23). [redacted] patients treated with ravulizumab across both studies were compliant with treatment as of the data cut-off date.

Table 23: Summary of treatment exposure data from ALXN1210-aHUS-311 and ALXN1210-aHUS-312: Extension Period up to data cut-off (Safety Set)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Ravulizumab Cohort 2 (n=10)
Treatment duration			
Mean weeks (SD)	[redacted]	[redacted]	[redacted]
Median weeks	[redacted]	[redacted]	[redacted]
[range]	[redacted]	[redacted]	[redacted]
Number of infusions, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
>16	[redacted]	[redacted]	[redacted]
Compliance, n (%)			
≥100%	[redacted]	[redacted]	[redacted]

Key: SD, standard deviation.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]

B.2.10.2 Adverse event data

Table 24 provides an overview of safety results as of data cut-off for ALXN1210-aHUS-311 and ALXN1210-aHUS-312. Key safety outcomes are summarized for each trial in turn below.

Table 24: Summary of safety results from ALXN1210-aHUS-311 and ALXN1210-aHUS-312: Extension Period up to data cut-off (Safety Set)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Ravulizumab Cohort 2 (n=10)
Patients with any AE, n (%)	[redacted]	[redacted]	[redacted]
Common adverse events[a], n (%)			
Headache	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]
Myalgia			

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Ravulizumab Cohort 2 (n=10)
AE severity, n (%)			
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]
Patients with any treatment-related AE, n (%)	[redacted]	[redacted]	[redacted]
Patients with any serious adverse event, n (%)	[redacted]	[redacted]	[redacted]
Common SAEs[b], n (%)			
Hypertension	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Malignant hypertension	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]
aHUS	[redacted]	[redacted]	[redacted]
Viral gastroenteritis	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Meningococcal infections, n (%)	[redacted]	[redacted]	[redacted]
Discontinuation due to AE, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Death due to AE, n (%)	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; aHUS, atypical haemolytic uremic syndrome; SAE, serious adverse event.
Notes: [a], Defined as ≥ 15% of patients – dashes represent events not meeting these criteria in individual trials/cohorts; [b], Defined as >1 patient – dashes represent events not meeting these criteria in individual trials/cohorts.
Sources: ALXN1210-aHUS-311 CSR[40]; ALXN1210-aHUS-312 CSR.[41]

B.2.10.2.1 ALXN1210-aHUS-311

Although all patients experienced an AE, most were medically manageable with only three patients discontinuing study due to an AE (autoimmune haemolytic anaemia, intracranial haemorrhage, immune TTP). The most common AEs were headache, diarrhoea and vomiting and the most common serious adverse events (SAE) were hypertension and pneumonia (Table 24). There were no cases of meningococcal infections.

Four patients died during the study (three who were included in the FAS and one further patient included in the safety analysis set), none of which were deemed related to study drug.[34] The three deaths in the FAS were the result of a fatal treatment-emergent AE: two patients died from septic shock and one patient died from a cerebral haemorrhage. The other patient who died suffered a cerebral artery thrombosis; this patient had been discontinued from the study after a single dose of ravulizumab due to differential diagnosis (positive STEC test), which is why they were only included in the safety analysis set (and not the FAS used for ITC and economic analyses). All these patients had significant comorbidities and presented in a critical state, with three receiving mechanical ventilation at baseline.

Clinical experts were asked to review narratives for all patients who died (see Appendix F) and give their opinion on the study investigator opinion that none were related to study drug at a recent UK advisory board.[24] They confirmed that the three patients in the FAS were high-risk at presentation and would probably not have been treated with complement-inhibitor treatment in UK clinical practice.[24]

Most AEs occurred within the Initial Evaluation Period with no additional SAEs, discontinuations or deaths observed in the Extension Period. An overview of safety results for the Initial Evaluation Period of ALXN1210-aHUS-311 is provided in Appendix F.

One treatment-emergent antidrug antibody (ADA) positive sample was observed but with low-titre, no neutralizing antibodies and no apparent effect on efficacy, safety or PK/PD.[34]

B.2.10.2.2 ALXN1210-aHUS-312

Although [redacted] in both cohorts experienced an AE, most were medically manageable with only [redacted] discontinuing study due to an AE ([redacted]).

The most common AEs in treatment-naïve patients were [redacted] and the most common SAEs were [redacted] (Table 24). The most common AEs in patients 'switching' from

eculizumab to ravulizumab were [redacted]; [redacted] SAEs were experienced in more than one patient (Table 24).

There were [redacted] cases of meningococcal infections across cohorts, and [redacted] patients died during the study (Table 24).

[redacted] treatment-emergent ADA positive samples were observed in [redacted].[41]

B.2.10.3 Safety overview

Ravulizumab treatment resulted in no unexpected AEs across the pivotal trial programme, demonstrating a comparable safety profile to eculizumab relating to their common mechanism of action. Indeed, all potential undesirable effects described in the ravulizumab SmPC are also listed as potential undesirable effects in the eculizumab SmPC.[25, 44]

A qualitative comparison of safety results across the treatment-naïve populations of pivotal ravulizumab and eculizumab trials used to inform the ITC is provided in Appendix F. The only clear difference between safety results are the number of deaths observed with no deaths across eculizumab trials, compared to the four deaths observed in the safety analysis set of ALXN1210-aHUS-311. As discussed previously, none of the deaths in ALXN1210-aHUS-311 were deemed related to study drug, and clinical experts in the UK considered those patients who died high-risk at presentation and unlikely to be treated with complement-inhibitor treatment in clinical practice.[24] Patients enrolled to the eculizumab trials are thought to better reflect patients who would be treated with complement-inhibitor treatment in UK clinical practice.[24] This difference is not therefore considered to represent a safety concern of ravulizumab compared to eculizumab; rather a difference in the underlying nature of disease of some individual patients enrolled across trials. Indeed, the EMA note that a similar safety profile is expected for ravulizumab and eculizumab, considering their shared mechanism of action.[39]

Important identified risks for eculizumab and ravulizumab include infections (meningococcal infections, aspergillus infections, sepsis, and other serious infections), infusion reactions, serious cutaneous adverse reactions, cardiac disorders and angioedema. Few events of this nature occurred in the ravulizumab

trial programme. The most important risk associated with C5 complement inhibition is increased susceptibility to infections caused by Neisseria meningitidis. This inherent risk with terminal complement inhibition has been well characterized with the use of eculizumab. To reduce the risk of infection, all patients must be vaccinated against meningococcal infections; patients who initiate treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with prophylactic antibiotics until 2 weeks after vaccination.[1] In the UK, the NRCTC advocate the use of long-term prophylactic antibiotics, and they are routinely prescribed throughout the duration of complement-inhibitor treatment. No cases of meningococcal infection were observed in the ravulizumab trial programme.

Overall, the conclusion of the EMA was that the safety profile of ravulizumab in aHUS appears to be comparable to that observed in adult patients with PNH, and that the safety profile in paediatric patients appears similar to that of adults.[39] The EMA had previously concluded that the safety profile of ravulizumab appears similar to that of eculizumab in patients with PNH, both in complement-inhibitor naïve patients and in patients clinically stable on eculizumab treatment.[45] Some differences in safety profiles were noted, namely the reported incidence of some events that seem to be higher in aHUS patients compared to PNH patients, which may be partly explained by the underlying disease, and the incidence of pyrexia, nasopharyngitis and constipation that seem to be higher in paediatric patients compared to adult patients.[39]

B.2.11. Ongoing studies

The Extension Periods of ALXN1210-aHUS-311 and ALXN1210-aHUS-312 are ongoing with further data expected towards the end of [redacted].

Regulatory review of two new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab is also ongoing with CHMP positive opinion received on 21 September 2020 and marketing authorization expected to extend to these vial sizes by November 2020. The increased drug concentration in these new vial sizes reduces the infusion times for ravulizumab. With the previous vial size (30 mL) containing 10 mg/mL of ravulizumab, the minimum infusion time ranged from 102–114 minutes for the loading dose and 120–140 minutes for maintenance doses in adult patients. With

the new vial sizes, the minimum infusion time for adults ranges from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses, bringing infusion times for adults treated with ravulizumab generally in line with those of eculizumab.[46] For paediatric patients, the minimum infusion times for ravulizumab 100 mg/mL vials range from 30–42 minutes for the loading dose and 42–72 minutes for maintenance doses. As the new vial sizes should be authorized prior to ravulizumab market launch in the UK (CHMP positive opinion received September 2020), they form the base case of the cost effectiveness analysis presented in Section B.3.

B.2.12. Innovation

Although ravulizumab was derived from eculizumab, small differences in their design have a substantial impact on health-related benefits for patients, carers and wider society. Ravulizumab provides immediate, complete and sustained terminal complement inhibition across an 8-week dosing interval (for patients above 20kg), reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase, compared with the 26 infusions needed for effective eculizumab treatment. For paediatric patients under 20 kg, 4-weekly dosing interval reduces the frequency of ravulizumab infusions compared with eculizumab to 13 per year.

The economic base case considers the impact of reduced infusion frequency on healthcare resources (cost savings) but not on patient quality of life. This is considered in a scenario analysis that utilizes discrete choice experiment (DCE) data from a UK population which reports a [redacted] utility gain for the reduced frequency of regular infusions with ravulizumab (100 mg/mL vial size) compared with eculizumab.[47] This is unlikely to capture the full potential benefit of the ravulizumab administration schedule compared with that of eculizumab, as the DCE descriptions did not consider potential complications of frequent treatment administration or the impact of frequency on daily living.

The need for frequent infusions puts patients' veins at risk of long-term damage and can result in a need for venous access ports in some patients, especially children, which subsequently puts them at risk of port-related complications.[48] The 'difficulty of access to veins' was the most frequently reported difficulty associated with eculizumab treatment in the 2016 Global aHUS Survey, and was similarly a common

theme across the PNH patient and carer interviews previously described (see Section B.1.3.3).[32, 33] The second most frequently reported difficulty associated with eculizumab treatment in the 2016 Global aHUS Survey and again a common theme across the PNH patient and carer interviews was the disruption to family life that the need for frequent infusions causes. For example, holidays must be limited to the period between infusions. Ravulizumab could reduce the risk of vein damage and minimize the disruption caused by the need for regular infusions.

The high frequency of regular infusions can also negatively impact children's education due to missed time at school. In the case of adults, it can negatively impact their work productivity due to missed time at work. Assuming a loss of earnings of £15/hour (based on full-time employee weekly earning reported for the UK[44]), eculizumab infusions cost each patient approximately £728 per year on average, while equivalent lost earnings for ravulizumab infusions are approximately £375 per year on average. This represents a potential gain of £353 per patient per year. Of course, for parents of paediatric patients who attend infusions and for informal carers of all patients who attend infusions, similar loss of earnings would apply. For patients who receive treatment in the hospital setting, lost earnings are likely to be even higher as travel and waiting times add to the total time needed for each infusion.

Wider societal benefits could additionally be incurred from increased productivity, as well as from the 'freeing-up' of healthcare professional time and healthcare resources that could be used to provide care elsewhere.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence

Across the pivotal trial programme, ravulizumab demonstrated similar efficacy to that previously demonstrated by eculizumab, which has transformed both the clinical prognosis of aHUS and the quality of life of patients.[4]

In adult patients who were complement-inhibitor naïve, over half of all those treated with ravulizumab achieved complete TMA response and over three-quarters achieved haematologic normalization. Furthermore, over two-thirds of patients

showed improvement in renal function (according to CKD staging), and of patients requiring dialysis at baseline, over half had discontinued within 6 months of ravulizumab initiation. An even higher proportion of paediatric patients who were complement-inhibitor naïve achieved these clinically meaningful outcomes with ravulizumab treatment. In patients who were clinically stable following ≥90 days treatment with eculizumab, 'switching' to ravulizumab did not impact haematological parameters, which remained clinically stable. Haematological normalization and improvements in renal function continued to be observed up to and beyond a year of treatment.

An ITC demonstrated no statistically significant or clinically relevant differences in effectiveness when formally comparing ravulizumab with eculizumab. A qualitative synthesis of pivotal trial data suggests no differences in safety profiles. Although both analyses highlighted that there were three deaths observed in the FAS of the ravulizumab trials compared with no deaths in the FAS of the eculizumab trials, none were deemed related to study drug and the patients who died had significant comorbidities and presented in a critical state. They would have been considered high-risk at presentation and as such would probably not have been treated with complement-inhibitor treatment in UK clinical practice.[24] No fatal AEs have been observed with ravulizumab in the PNH setting.[49, 50]

An assumption of equivalence is strongly supported when considering the technologies share over 99% homology and the same fundamental mechanism of action. Differences that are seen in their design do not impact the clinical effectiveness or safety of ravulizumab compared to eculizumab, but rather allow a natural recycling of complement-inhibitor that extends its half-life and reduces the frequency of regular infusions (see Section B.2.12). Non-inferiority has been formally assessed in the PNH trial programme where ravulizumab was shown to be statistically non-inferior to eculizumab.[49, 50]

Taking all these factors into consideration, despite the absence of head-to-head data, the EMA accepted that comparative efficacy has been substantiated in the adult population and the clinical community consulted in the UK is confident that ravulizumab has similar efficacy and safety to eculizumab.[24, 39]

B.2.13.2 Strengths and limitations of the evidence base

B.2.13.2.1 Applicability of the evidence base to the decision problem

The pivotal trial programme supporting the use of ravulizumab consists of two single-arm studies and therefore does not provide head-to-head data of relevance to the decision problem. As concurred by the EMA, the lack of a comparator arm is considered acceptable bearing in mind the low prevalence of aHUS and the severity of the condition.[39] The sample size for a randomized, active-controlled non-inferiority study would need to have been at least twice as large and have required twice as many sites; as noted by the EMA, conducting a non-inferiority trial with >300 centres and >100 patients would be prohibitive.[39] A comprehensive series of ITCs have been conducted to fill this evidence gap with consistency of outcomes across base case and sensitivity analyses supporting the robustness of conclusions made.

The outcomes assessed in ALXN1210-aHUS-311 and ALXN1210-aHUS-312 were chosen to represent the health-related benefits and potential side-effects expected with ravulizumab treatment in practice. They encompassed the continuum of disease pathophysiology from the biochemical (change in free C5), to downstream haemolytic parameters (LDH and platelet normalization), to clinical outcomes (renal function and dialysis), safety outcomes, and HRQL outcomes. The clinical community confirmed that the trial outcomes represent outcomes measured in clinical practice to assess response to treatment.[24]

B.2.13.2.2 Generalizability of trial populations to patients in clinical practice

In the absence of a single known cause, aHUS remains a diagnosis of exclusion, making it more complex to align trial eligibility criteria to real-word patient characteristics. The clinical community believe the ALXN1210-aHUS-311 trial population is slightly broader than patients who would receive eculizumab in UK practice.[24] They specifically note a smaller proportion of patients with a known complement regulatory gene/protein mutation or anti-CHF autoantibody (20.5%[34]) than reported for the real-world population (45–70%[6-9]). This was not the case in the eculizumab clinical trial programme, where the proportion of patients with a known complement regulatory gene/protein mutation or anti-CHF autoantibody ranged from 49–76%.[28-30]

Those that would be less likely to be treated with complement-inhibitor treatment in UK practice generally had the worse outcomes, including those patients who died in ALXN1210-aHUS-311. Their inclusion would therefore bias against ravulizumab. If used to treat the same patient population in UK clinical practice, ravulizumab would be expected to provide comparable health benefits to eculizumab.[24]

There was also a high proportion of Asian patients enrolled to the clinical trial programme, and lower rates of complete TMA response were noted among Asian patients (see Appendix E). This is thought to be related more to management and diagnostic differences at the South Asian sites, rather than a reflection of ethnic variance, but this could further bias against ravulizumab when applying trial outcomes to expected effectiveness in UK clinical practice. In an ITC sensitivity analysis that excluded Asian patients, an increased proportion of patients had a complete TMA response and improved CKD stage compared to the base case analysis (see Appendix D).

B.2.13.2.3 Evidence for patients responsive to eculizumab

'Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab'.

Evidence for patients responsive to eculizumab is available from a cohort of paediatric patients with clinically stable disease following ≥90 days treatment with eculizumab 'switching' to ravulizumab (Cohort 2 of ALXN1210-aHUS-312). Supportive evidence for the safe 'switching' of patients can be taken from the use of ravulizumab in the PNH setting. In the ALXN1210-PNH-302 trial, adult patients with PNH who were clinically stable following ≥ 6 months treatment with eculizumab (n=197) were randomized to continue receiving eculizumab or 'switch' to ravulizumab.[49] Ravulizumab was shown to be statistically non-inferior to eculizumab across all efficacy endpoints, and the study concluded that patients may be safely and effectively 'switched' from eculizumab to ravulizumab.

Based on these results, the EMA concluded that the indication for patients with aHUS could include patients who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.[39] The extrapolation of the indication to a population of patients refractory to eculizumab treatment is not supported, and this is not the intended positioning of ravulizumab (see Section B.1.3.2).

B.2.13.2.4 Ravulizumab infusion in trials compared with clinical practice

At the time of trial initiation, only the 30 mL vial size containing 10 mg/mL of ravulizumab was available, and all patients enrolled to ALXN1210-aHUS-311 and ALXN1210-aHUS-312 were thus infused according to minimum infusion times recommended for this concentration of the drug.

At the time of market launch of ravulizumab in the UK, new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab are expected to be authorized and will supersede use of the 30 mL vial. The new vial sizes offer reduced infusion times (see Section B.2.11) that are expected to have a quality of life benefit that the trial HRQL data would not have captured. Importantly, there are no pharmacokinetic differences observed across vial sizes such that the pharmacodynamic effects including clinical efficacy and safety outcomes will be maintained with the new vial sizes, while infusion times are aligned to those for eculizumab, but with the significantly reduced infusion frequency offered by ravulizumab.

B.2.13.3 Clinical effectiveness conclusion

Ravulizumab offers immediate, complete and sustained terminal complement inhibition, and benefits patients and carers by reducing the treatment burden compared with eculizumab, while maintaining clinical effectiveness. Ravulizumab thus addresses some remaining areas of unmet need in the aHUS setting.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A combined systematic review of the published literature was conducted to identify all relevant economic evaluations/modelling studies, HRQL studies and costs and resource use publications for the treatment of patients with aHUS. Full details of the search strategy are provided in the Appendix G.

The search was originally conducted on 12 March 2019. It was updated on 3 April 2020 using the following electronic databases:

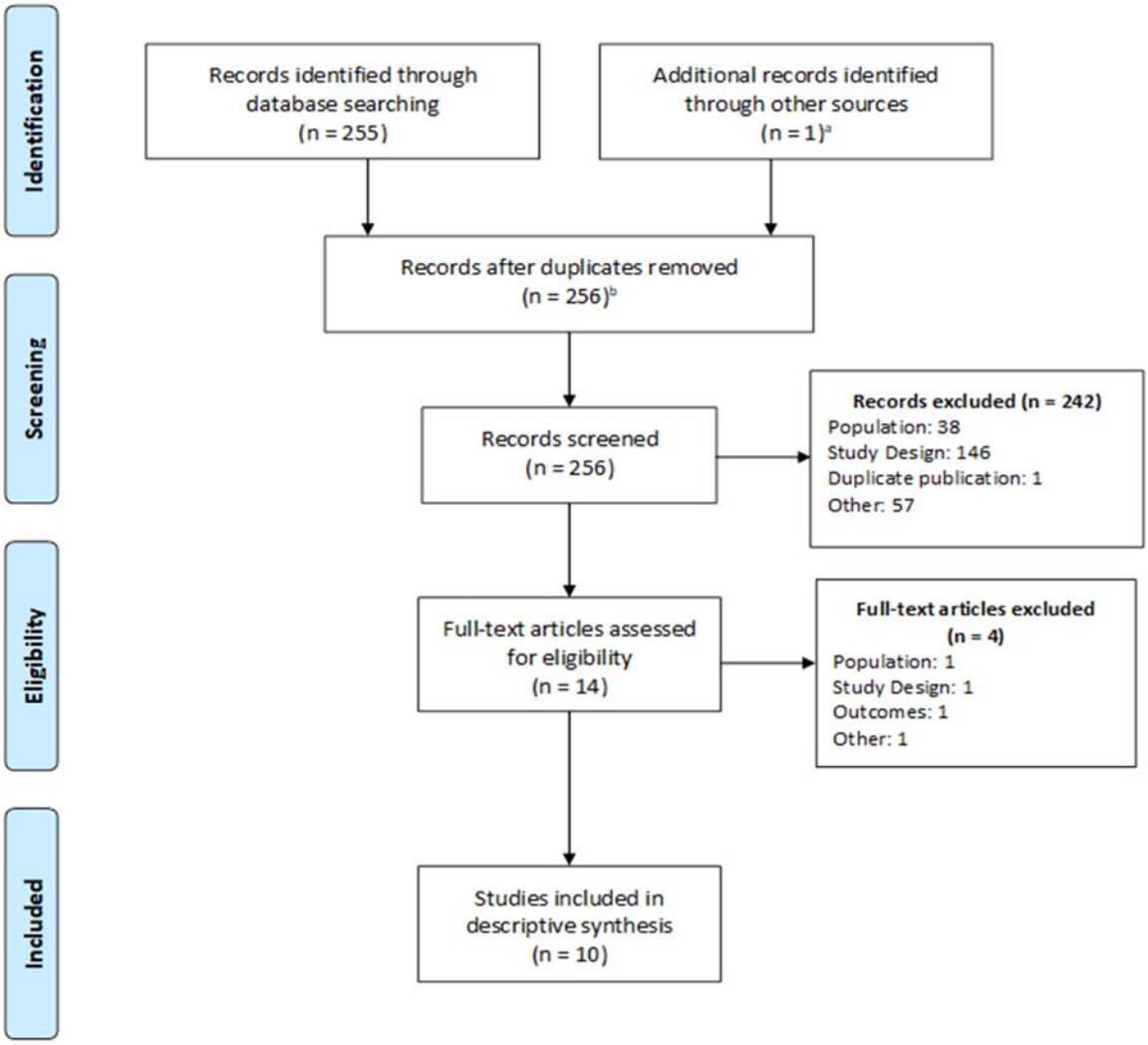
- MEDLINE® and MEDLINE® In-Process
- Embase®
- EconLit® (assessed via EBSCOhost)
- The Cochrane Library, including the following:
  - Database of Abstracts of Reviews of Effects (DARE)
  - NHS Economic Evaluation Database (NHS EED)
  - Health Technology Assessment Database (HTAD)

Note: Additionally, EconLit was assessed via EBSCOhost.

Additionally, conference abstracts from the most recent 2 years (2017 to the date of the original search) were included to capture research not yet published as manuscripts. Conference abstracts identified in the updated search were also reviewed for relevance.

The details for the studies identified, including those from both the original and the updated search, are presented in Figure 15 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 15: PRISMA flow diagram for the economic studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Notes: [a], Grey literature; [b], Removal of duplicates was built into the strategy.

Of the 10 studies included in the combined economic review, three papers discussed two cost-effectiveness analyses: one in the UK for an aHUS population[16, 51] and one in the Netherlands for an aHUS population with ESRD.[52] The remaining seven studies reported HRQL or costs. The published cost-effectiveness analyses are summarized in Table 25.

Table 25: Summary of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Tappenden 2013, NICE 2015 (HST1)	2013	State-transition model with five health states: CKD 0–2, 3–4, 5, transplant and death	aHUS (28 years)	Total QALYs: Eculizumab: 30.99 Standard care: 5.77 Incremental: 25.22	Total costs: Eculizumab: [redacted] Standard care: £322,313 Incremental: [redacted]	No ICERs reported from the analysis[a]
Van Den Brand, 2017	2017	State-transition Markov model looking at different treatment pathways for patients with aHUS with ESRD	aHUS with ESRD	Transplantation without eculizumab: 8.34 Dialysis: 3.73 Eculizumab upon recurrence: 9.55 Eculizumab induction: 9.53 Eculizumab lifelong: 9.36	Transplantation without eculizumab: €402,412 Dialysis: €406,897 Eculizumab upon recurrence: €425,097 Eculizumab induction: €918,347 Eculizumab lifelong: €5,441,576	€18,748 per QALY (for kidney transplantation with eculizumab upon recurrence of aHUS)

Key: aHUS, atypical haemolytic uraemic syndrome; CKD, chronic kidney disease; ESRD, end-stage renal disease; HST, highly specialized technology; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHS, National Health Service; NICE, National Institute of Health and Care Excellence.
Notes: [a] Makes reference to an NHS England commissioning policy that reports £521,000 per QALY gained for a 23-year-old cohort of patients; For a 2-year-old cohort of patients it was £376,000 per QALY gained.[53]

The UK model was reported in the Evidence Review Group's (ERG's) appraisal of the economic evidence submitted to NICE (HST1), which describes the analysis of the costs and benefits of eculizumab compared with standard care.[16, 51]

This is the only model identified in the review that is relevant to our decision problem. The model uses a state-transition model (Markov cohort) and has five mutually exclusive health states that consider a patient's kidney function (CKD 0–2, 3–4 and 5), a temporary health state for those who undergo transplant and a death state.

For the eculizumab group, transitions to better or worse CKD health states were possible in any model cycle. Eculizumab-treated patients have the same risk of death as the general population, unless they develop ESRD (CKD 5). In the standard care group, only transitions to worse health states were possible, except when transplantation was assumed to be successful. Plasma therapy-treated patients suffer a constant additional risk of death due to aHUS, irrespective of their CKD level. Transitions to the transplant health state were assumed to apply only to the standard care group.

The Committee recommended eculizumab, based on the HST1 submission and ERG analyses for funding as an aHUS treatment, under the following conditions: arrangements of coordinated eculizumab use through an expert centre, monitoring systems to record the number of people with a diagnosis of aHUS and who have eculizumab, a national protocol for starting and stopping eculizumab and a research programme to evaluate when stopping treatment might occur. Both analyses by the ERG and manufacturer produced substantial quality-adjusted life year (QALY) gains of a magnitude that is rarely seen for any new drug treatment.

B.3.2. Economic analysis

The analysis presented in this submission is adapted from the HST1 model, taking into account feedback from the ERG and NICE. The ERG had several concerns regarding the key assumptions made within the model and the derivation of some of the efficacy inputs. A detailed description of this feedback, and its consideration in this analysis, is presented in Table 26.

Table 26: Feedback from HST1 model and changes made for this analysis

Issue	Critique	How this is addressed in this analysis
Discount rate	Discount rate of 1.5% was applied in the previous model base case vs discount rate of 3.5% specified in the reference case. This was criticised by the ERG but accepted by the committee.	Discount rate of 3.5% has been applied in the base case in line with the reference case for an STA because the comparison is conducted vs another active treatment that restores people to near full health rather than to supportive care.
Population	Only considered an adult population but included a lower dose for children. The model population began with a cohort of patients aged 28 years, which drove the time horizon of the model and background mortality. The model also included dose reductions for patients who are assumed to be children on entry into the model. This approach was criticized as being conceptually inconsistent as it modelled the prognosis of adult patients but included dose-reductions for paediatric patients.	The model considers both adults and children separately, but the results are presented together by combining the individual results. To address the range of ages, dosing calculations are informed by age/weight distributions. Similarly, background mortality is based upon an age distribution instead of a mean starting age.
Costs/Perspective	Perspective seems to be NHS only and does not include PSS costs.	This submission includes resource use costs, which were validated at the UK advisory board. PSS costs have been included where possible (e.g. administration).
Adverse Events	The eculizumab studies reported in C11-003 included three deaths and several complications that may indicate that treatment with eculizumab does not fully eliminate the risk of non-renal aHUS complications. The manufacturer's model was criticized for not including any adverse events for eculizumab in comparison to supportive care.	Adverse events have not been included in the model. Given that the relevant comparator is eculizumab, the adverse event profiles are similar, and this is no longer considered relevant.
Utilities	Using study-derived HRQL values was considered to potentially overestimate the benefit of eculizumab. Using a value of 1.0 for the health state CKD 0–2 is higher than the UK general population EQ-5D norms. The Committee felt that it was likely that other benefits of a substantial nature had not been adequately captured in the model, and therefore, may have caused underestimation of the overall effectiveness of eculizumab.	Given the similarity between treatments, utilities are not considered in the base case analysis. In the scenario looking at different effectiveness, utilities have been capped against general population norms and age-related utility decrements are applied per cycle. Uncaptured benefits due to lack of data are assumed to be less of an issue as these would be expected to be of similar magnitude for ravulizumab and eculizumab.

Issue	Critique	How this is addressed in this analysis
Modelling discontinuations	In line with the eculizumab marketing authorization, the previous model envisaged lifelong treatment with eculizumab for patients with aHUS, with treatment discontinuations largely limited to adverse events.	Clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard. The model reflects discontinuation in current UK clinical practice based on early discontinuations related to differential diagnoses, non-response to treatment, renal recovery/stabilization or other reasons (e.g. safety, pregnancy, patient choice).
Pooling of potentially heterogeneous study populations	The model used simple pooling of patient-level data from studies C08-002A/B and C08-003A/B to inform transition probabilities for both treatment groups. It was unclear whether this was appropriate.	Based on evidence supporting the same efficacy between treatments, equal effectiveness is modelled in the base case. As a scenario, differential efficacy is modelled. As there are no head-to-head data available for ravulizumab and eculizumab, the scenario model uses the ITC reported in Section B.2.9 to estimate relative efficacy. The ITC is limited by small sample sizes and heterogeneity across the different studies (see Appendix D.1.4). Additionally, only CKD stage information is taken forward into the model, whereas for other endpoints the ITC shows mostly benefit for ravulizumab vs eculizumab.
Use of restrictive model structure	The ERG had concerns with respect to the restrictive nature of the manufacturer's model structure. For both eculizumab and standard care groups, the model applied a single fixed-transition matrix, thus structurally imposing an assumption that CKD transition probabilities in both groups are time-invariant (excluding mortality effects).This was considered a highly restrictive assumption that does not make the best use of the available evidence.	In the scenario looking at differential efficacy from the ITC, time-dependent transition probabilities are calculated based on the ordinal probit models up to 1 year. Transitions are assumed constant after 1-year.
Problems of derivation of transition matrices	The ERG had several issues with the derivation of transition probabilities in the HST1 model, including inappropriate handling of competing risks.	In the scenario looking at differential efficacy from the ITC, CKD transition probabilities are now estimated using the multi-state modelling approach.

Key: CKD, chronic kidney disease; ERG, Evidence Review Group; HRQL, health-related quality of life; HST, highly specialized technology; ITC, indirect treatment comparison; PSS, Personal Social Services; STA, single technology appraisal.

As discussed in Section B.1.2, ravulizumab (ULTOMIRIS®) was developed to share over 99% homology with eculizumab; therefore, there is reason to consider that ravulizumab and eculizumab have similar efficacies. While no head-to-head trial in aHUS is available to confirm this assumption, the results from the ITC, using propensity score weightings, demonstrate no significant, systematic or clinically relevant differences between treatment arms. This was shown to be the case for all subpopulations analysed (see Section B.2.9). While there are limitations with the ITC data and trial populations[24], discussed in Section B.2.9, evidence from two head-to-head Phase III trials in patients with PNH, which were designed to assess the non-inferiority of ravulizumab compared to eculizumab, show that ravulizumab is non-inferior to eculizumab and has similar efficacy and safety outcomes.[49, 50] Considering all these factors, despite the absence of head-to-head data, the EMA accepted that comparative efficacy has been substantiated in the adult population and the clinical community consulted in the UK is confident that ravulizumab has similar efficacy and safety to eculizumab.[24, 39]

Based on this evidence, the economic analysis base case assumes that the two treatments are equally effective. The base case, which assumes that all efficacy is the same between treatment arms, only compares the differences in treatment costs. A scenario analysis considering differential effectiveness is also presented as a worst-case scenario. The worst-case scenario, based solely upon CKD stage outcomes from the ITC, models the differences between health states and captures the differences between life years, QALYs and costs. This is presented as a single technology appraisal (STA) and not a fast-track appraisal (FTA), was requested by NICE.

This document presents all the information relevant to the model base case, which assumes equal effectiveness. Additional details of the scenario analysis, assuming differential effectiveness, are presented in Appendix N.

B.3.2.1 Patient population

The patient population considered is in line with the license: adults and children 10 kg or above with aHUS who are complement-inhibitor treatment-naïve or have

received eculizumab for at least 3 months and show evidence of response to eculizumab.

The model explicitly considers treatment-naïve patients due to the lack of evidence on patients who have switched from eculizumab. However, patients who have switched are assumed to have the same outcomes as treatment-naïve patients.

The model considers adults and children separately due to the multiple evidence sources and expected cost differences due to differing weights. For the base case analysis, patient characteristics are based on the pooled eculizumab and ravulizumab trial data in the ITC analysis (using the weighted values, see Section B.2.9). A summary has been provided in Table 27. It is important to note that four patients in the ALXN1210-aHUS-312 trial were under 10 kg (6.9 kg, 8.5 kg, 8.8 kg and 9.1 kg). However, one patient was not included in the FAS due to a positive Shiga toxin test (6.9 kg). Additionally, four patients in the C10-003 eculizumab trial were under 10 kg (6.7 kg, 8.3 kg, 8.5 kg and 9.9 kg). Despite these patients not being included within the licensed patient population, they were included in the ITC due to the small patient numbers available for analysis. As most of these patients are close to 10 kg, it is unlikely that their inclusion will impact the direction of the results. However, removal of these patients from the ITC would increase uncertainty due to the small numbers of patients available for analysis in this ultra-orphan population. Despite this, to reflect the characteristics of the population expected to receive ravulizumab, these patients are not included in the dataset used for patient characteristics within the analysis.

Using weight data specific to European patients was considered; however, as the weight for European patients in the trials was similar to the full population (mean 73.1 kg and 72.8 kg, respectively, for adult patients and 25.3 kg and 24.3 kg, respectively, for children), it was decided to use data from the full trial population.

Table 27: Baseline patient demographics by population

Patient demographic	Adults	Children	Source
Age, mean	[redacted]	[redacted]	311
Percentage female	[redacted]	[redacted]	312
Weight, mean (kg)	[redacted]	[redacted]	C08-002
Weight distribution			C10-003
≥ 10 to < 20	[redacted]	[redacted]	C10-004
≥ 20 to < 30	[redacted]	[redacted]	
≥ 30 to < 40	[redacted]	[redacted]	
≥ 40 to < 60	[redacted]	[redacted]	
≥ 60 to < 100	[redacted]	[redacted]	
≥ 100	[redacted]	[redacted]	
CKD stage distribution			
0–2	[redacted]	[redacted]	
3a–3b	[redacted]	[redacted]	
4	[redacted]	[redacted]	
5/ESRD	[redacted]	[redacted]	

Key: CKD, chronic kidney disease; ESRD, end-stage renal disease.

B.3.2.2 Model structure

As discussed in Section B.3.1, the previous model for eculizumab in HST1 used a state-transition model, with health states based around kidney function and transplant. This model was designed to simulate the experience of patients with aHUS receiving eculizumab or standard care. There was no direct critique relating to the model structure within HST1, and the health states are considered representative of the aHUS pathway.

Renal damage in patients with aHUS varies and is classified according to CKD stages. As per clinical guidelines, CKD is defined by the presence of kidney damage or decreased kidney function for 3 or more months, irrespective of the cause. Persistence of the damage or decreased function for at least 3 months is necessary to distinguish CKD from acute kidney injury.[54] Transplants are also an important feature of the aHUS pathway, although since the availability of eculizumab the transplant rate has decreased.[19] As such, the model structure presented in HST1 seemed appropriate to represent the aHUS pathway and was therefore taken forward in this analysis. In addition to health states capturing CKD stage and

transplant, treatment discontinuation was considered an important part of the clinical pathway for patients on complement C5 treatment; therefore, it is explicitly modelled in this submission. In the HST1 submission model, discontinuation was not explicitly modelled because it envisaged lifelong eculizumab treatment and treatment discontinuation was limited to discontinuation caused by AEs. Clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard for all patients.

A cohort state-transition model was developed that included health states around treatment discontinuation and subhealth states, reflecting aHUS-associated renal function and transplant.

A cohort-transition model is considered appropriate if patient prognosis does not demonstrate sufficiently important individual heterogeneity. The clinical literature was reviewed to identify patient characteristics driving major outcomes, such as the impact of age of presentation and complement-related mutations. The literature review indicated that there may be meaningful differences in the prognoses of children versus adults presenting with aHUS. As described in the Rathbone et al. (2013)[55] literature review, observational data suggest that the mortality rate is higher in children than in adults, but progression to ESRD is more frequent in adults. Beyond age at presentation, a degree of heterogeneity in prognosis in the first 1–3 years of disease has been observed relating to underlying mutation types associated with aHUS. However, with the exception of membrane cofactor protein-related mutations, rates of progression to ESRD are similar, as observed by Fremeaux-Bacchi et al. (2013).[6] Data from patient registries show no systematic differences in aHUS prognosis between patients with and without an identified pathogenic variant.[56] Finally, recent research has sought to determine the predictors of CKD progression among patients with aHUS. For instance, Jamme et al. (2017) found that a high serum creatinine level, a high mean arterial pressure, and a mildly decreased platelet count are predictive of CKD, consistent with the pathophysiology of kidney damage in aHUS.[57] However, Jamme et al. concluded that while their model accurately predicts development of 1-year CKD in patients, further validation is required before it may be applied in clinical practice.

In light of the considerations above, it was deemed that a cohort state-transition model with analyses conducted separately for children and adults would be most appropriate for informing reimbursement decision making. While progression of aHUS in an individual patient may occur in 'episodes', due to uncertainty around the incidence of such episodes, modelling to match clinical study observations of CKD outcomes was deemed preferable.

Clinical studies of ravulizumab and eculizumab for aHUS did not restrict enrolment based on genetic abnormalities. As such, transitions that are modelled based on clinical study data should be viewed as reflecting a mix of patients with and without mutations and not specifically accounting for the differences.

The model structure consists of four main health states: initiate treatment, discontinuation, relapse and reinitiate treatment. Within each health state, there are eight subhealth states describing aHUS progression: CKD Stage 0–2, 3a–3b, 4, 5/ESRD, transplant, transplant success, excess death and background death (as demonstrated in the 'initial treatment' health state in the model diagram in Figure 16). CKD Stages 0, 1 and 2 were pooled as CKD 0–2 and CKD Stage 3a and 3b were pooled as these groups would have minimal differences in costs[58] and utilities and there were small numbers in the individual groups. Clinicians felt that the model structure appeared to accurately reflect the potential for both improvement and deterioration across CKD stages and agreed that the model structure seemed appropriate.[24]

The 311 and 312 trial endpoints for CKD stage are evaluated by eGFR at select days (see Table 28). As such, CKD stage was modelled based on eGFR data collected in the eculizumab and ravulizumab trials and defined using classifications based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines (see Table 28).[59] In the eculizumab studies, CKD Stage 0 was recorded based on the classification system developed by the US National Kidney Foundation and reported by Levey et al. (2003).[60] It is defined as ≥ 60 mL/min per 1.73 m^2 with CKD risk factors.

Table 28: CKD stage definitions (KDIGO 2012)[59]

CKD stage	eGFR (mL/min/1.73 m^2)	Terms
1	≥ 90	Normal or high
2	60–89	Mildly decreased
3a	45–59	Mildly to moderate decreased
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5	< 15	Kidney failure

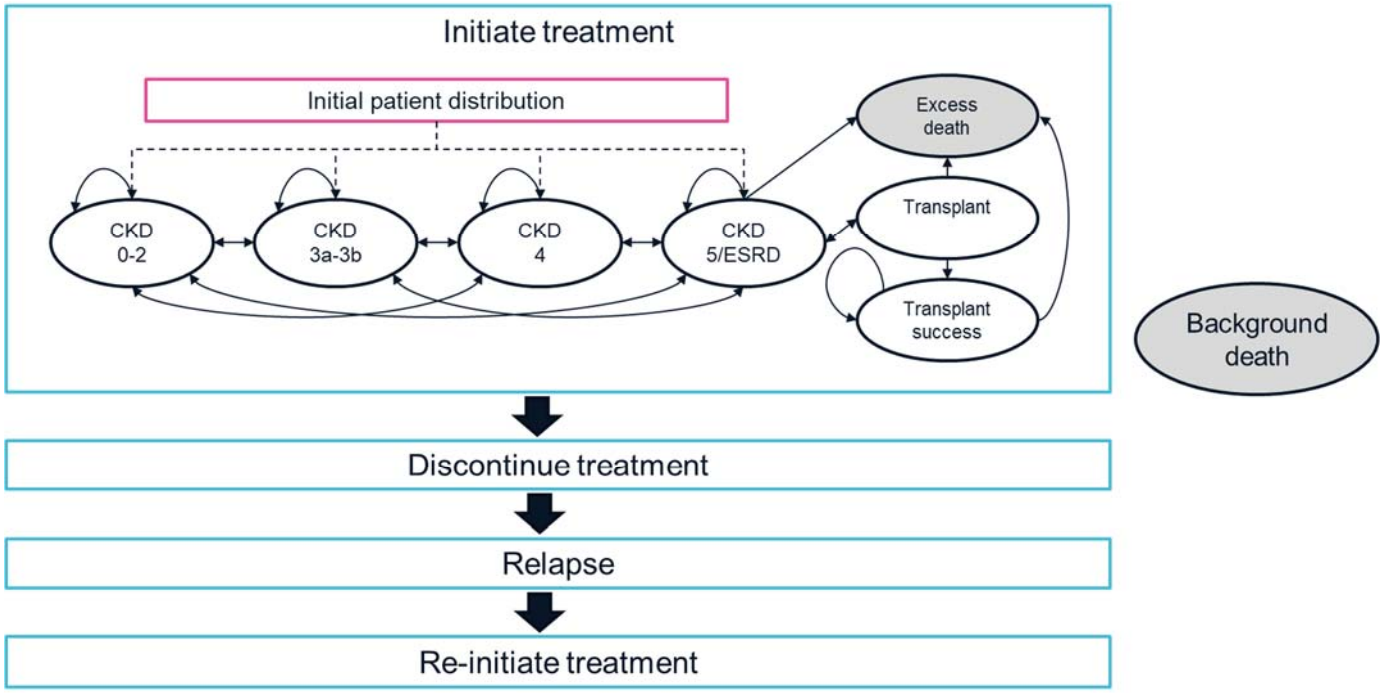
Key: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

Transitions to transplant, transplant success and death due to aHUS are modelled from the literature due to a lack of data from clinical trials. Only patients who are within the CKD 5/ESRD state can transition to the transplant subhealth state, which acts as a tunnel state while they undergo a transplant for one model cycle. Patients are then either deemed successful and transition to 'transplant success' or deemed a 'failure' and transition back to CKD 5/ESRD or die (excess death) from their transplant. Excess death includes increased mortality from aHUS CKD 5/ESRD, transplant surgery or post-transplant, whereas background death represents general population mortality that can occur from any health state at any time.

Treatment discontinuation can happen at any time in the model based on numerous reasons (see Section B.3.3). Given the variation of discontinuations in clinical practice and based on individual patient circumstances, various sources and scenarios are considered. Figure 16 presents the model structure diagram.

The same model structure is used in the base case and scenarios with differential efficacy; however, in the base case, transitions through CKD stages are assumed the same for both arms because the ITC showed no systematic, significant or clinically relevant differences between treatments.

Figure 16: Economic model diagram



Key: aHUS, atypical haemolytic uremic syndrome; CEA, cost-effectiveness analysis; CKD, chronic kidney disease; ESRD, end-stage renal disease
Notes: Excess death includes the increased mortality risk from aHUS, ESRD, transplant surgery and post-transplant, whereas background death accounts for the natural risk of mortality associated with age. Transitions to background mortality may occur from any living health state. Dashed black arrows represent patients' entry into the CEA model. Solid black arrows represent transitions possible in the model. **Blue boxes represent the main health states; each of these are split into the disease-specific subhealth states as shown in the 'Initiate treatment' health state.**

Table 29 summarizes the key features of the economic analysis compared to HST1, the previous appraisal in the same disease area within the aHUS setting.

As per the NICE reference case, a 3.5% discount rate (DR) was used for costs, and the perspective is of the NHS and Personal Social Services (PSS). A cycle length of 14 days is used in the model. This captures the dosing frequency of eculizumab and is considered sufficiently short to accurately capture key clinical outcomes and dosing regimens. Given the relatively short cycle length, half-cycle correction is not applied.[61]

The model time horizon considers a patient's lifetime and runs for a maximum of 100 years. Given that the population considers some patients younger than a year old, 100 years captures the full lifetime of all patients. The model assumes that all

patients die at age 100. Shorter time horizons are tested in scenario analysis (see Section B.3.8).

Table 29: Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**HST1[16]**	**Chosen values**	**Justification**
Time horizon	100 years, lifetime horizon	100 years, lifetime horizon	Chronic disease so important to capture a patient's lifetime
Model structure	State-transition	State-transition	Accurately capture transitions between health states to reflect the aHUS clinical pathway and make use of available data
Discontinuation	Not captured because the model envisaged lifelong treatment	Various sources to capture different reasons for patients discontinuing, including trial data	Variation in why patients discontinue in clinical practice versus trial data. There is also variation in clinical practice between patients
Source of costs	Dialysis and transplant costs were included based upon HRGs. CKD stage costs for monitoring and medications were included based upon published literature	Literature sources used for disease-specific monitoring costs. Treatment-specific costs based on clinical opinion	These were chosen to reflect monitoring of patients with aHUS in clinical practice. Clinical opinion used due to lack of aHUS-specific guidance

Key: aHUS, atypical haemolytic uremic syndrome; CKD, chronic kidney disease; HRG, Healthcare Resource Group; HST1, highly specialized technology 1.

B.3.2.3 Intervention technology and comparators

The ravulizumab dosing schedule within the model is based on the license and is summarized in Table 30. Depending on a patient's weight, a loading dose is given via intravenous infusion followed by the first maintenance dose 2 weeks after the loading dose and subsequent maintenance doses every 8 weeks. Children between 10 and 20 kg receive the maintenance dose every 4 weeks, while those over 40 kg receive their maintenance dose every 8 weeks (the same as adults). The dosing

schedule for ravulizumab is consistent with the dosing schedules within the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 clinical trials.[40, 41]

The comparator considered in the model is eculizumab, a complement C5 treatment that was approved for use in aHUS by NICE in 2015.[16] As discussed in Section B.1.3, eculizumab is the current standard of care in UK clinical practice.

Eculizumab dosing in the model is in line with the SmPC schedule[25]; for adults and children over 40 kg, this consists of 900 mg every week for the first 4 weeks then 1,200 mg for the fifth week followed by 1,200 mg every 2 weeks via intravenous infusion. Doses for children under 40 kg vary by weight (summarized in Table 30).

Table 30: Model intervention and comparator with dosing schedules

Treatment	Population	Body weight (kg)	Dose	Source
Ravulizumab	Adults	≥ 40 to < 60	2,400 mg followed by 3,000 mg every 8 weeks	SmPC[1]
		≥ 60 to < 100	2,700 mg followed by 3,300 mg every 8 weeks	
		≥ 100	3,000 mg followed by 3,600 mg every 8 weeks	
	Children[a]	≥ 10 to < 20	600 mg followed by 600 mg every 4 weeks	
		≥ 20 to < 30	900 mg followed by 2,100 mg every 8 weeks	
		≥ 30 to < 40	1,200 mg followed by 2,700 mg every 8 weeks	
Eculizumab	Adults	NA	900 mg weekly for four doses and 1,200 mg for the fifth week followed by 1,200 mg every 2 weeks	SmPC[25]
	Children*	≥ 10 to < 20	600 mg weekly for one dose followed by 300 mg every 2 weeks	
		≥ 20 to < 30	600 mg weekly for two doses followed by 600 mg every 2 weeks	
		≥ 30 to < 40	600 mg weekly for two doses followed by 900 mg every 2 weeks	

Key: SmPC, summary of product characteristics; kg, kilograms; NA, not applicable.
Note: [a] Children over 40 kg have the same dosing schedule as adults.

B.3.3. Clinical parameters and variables

As discussed in Section B.2.13.1, the ITC demonstrated no systematic, statistically significant or clinically relevant differences in effectiveness when formally comparing ravulizumab with eculizumab. A qualitative synthesis of pivotal trial data suggests no differences in safety profiles. Assuming equivalence is strongly supported when considering that the technologies share over 99% homology and the same fundamental mechanism of action. Non-inferiority was formally assessed in the PNH trial programme and ravulizumab was shown to be statistically non-inferior to eculizumab.[49, 50] Moreover, despite the absence of head-to-head data, the EMA accepted that comparative efficacy has been substantiated in the adult population and the clinical community consulted in the UK is confident that ravulizumab has similar efficacy and safety to eculizumab.[24, 39] As such, the base case assumes the same efficacy and safety between eculizumab and ravulizumab and only considers differences that impact treatment costs.

A scenario analysis is also presented that models the differences between efficacy using the ITC data. This is considered a worst-case scenario as only one endpoint (which by chance favours eculizumab) is carried forward from the ITC. For the equal efficacy analysis, all health state occupation inputs for ravulizumab were assumed to be the same as per eculizumab. Further details of the clinical inputs used to inform health state occupation in this analysis are presented in Appendix N.

B.3.3.1 Treatment discontinuation

According to the eculizumab and ravulizumab SmPCs, patients with aHUS should only discontinue treatment if medically justified as there are no specific data on treatment discontinuation.[1, 25] The SETS study is currently investigating safety and impact in patients who discontinue eculizumab (as recommended in the HST1 outcome); this will likely inform how and when patients can discontinue therapy (see Section B.1.3.2).[62] In a long-term prospective observational study, discontinuation of eculizumab resulted in a 13.5-fold higher rate of thrombotic microangiopathy recurrence and showed a trend toward reduced renal function compared with patients who continued treatment.[63] Therefore, until the results of the SETS study are produced, clinicians are hesitant to discontinue long-term maintenance therapy

in patients with aHUS unless there is a clear clinical need identified or knowledge of which patients would be suitable for discontinuation.

In the aHUS clinical trials, patients could only discontinue treatment if they suffered from AEs, become pregnant or based on clinical judgement.[40, 41] Additional criteria for discontinuation from the eculizumab trials include aHUS crisis, disease progression and newly developed antimicrobial resistance.[64-67]

In clinical practice, patients can discontinue eculizumab treatment for numerous reasons, many of which depend on individual patient circumstances and needs. These can be grouped into four categories:

- Patients who initially start treatment but are found to have a differing diagnosis:
  - Patients presenting with aHUS symptoms are treated while tests are conducted to confirm the diagnosis. Additionally, screening for differential diagnosis continues, including screening for STEC-HUS and thrombotic thrombocytopenic purpura in children
  - Some patients do not respond to treatment and have a different diagnosis once test results return
  - The NRCTC service aims to complete screening within 1 month of treatment initiation, although in practice this will vary and test results may come sooner or later[24]
  - The NRCTC reports show that between 2016 and 2019, on average, 17% of patients initiated on eculizumab discontinue due to differential diagnosis[19, 68, 69]
- Patients who have no renal recovery after treatment:
  - These patients are assumed to either not have complement-mediated aHUS or have been initiated on treatment too late for complement-inhibitor treatment to be effective
  - Discontinuation in this group usually happens approximately 3–4 months after treatment initiation for patients on eculizumab[24]
  - The NRCTC reports show that between 2016 and 2019, on average, 23% of patients discontinued treatment due to lack of renal recovery[19, 68, 69]
- Patients who do have renal recovery and are discontinued based on low risk of recurrence or patient preference:

- These patients will have achieved stabilization if not normalization of renal function and are considered for discontinuation on a case-by-case basis
- Currently, patients being considered for discontinuation for this reason are enrolled to the SETS study, which is designed to assess the safety and impact of eculizumab withdrawal
- This could occur at any time point after the first month of treatment and confirmed diagnosis. The KDIGO guidelines recommend discontinuing on a case-by-case basis after at least 6–12 months of treatment and at least 3 months of normalized kidney function.[5] Current clinical opinion seems to suggest that patients do not discontinue for at least 12 months if they respond well to treatment, unless they enrol onto the SETS study
- There are little data to inform how many patients may discontinue for these reasons in future clinical practice given that this is not current standard practice. The NRCTC report shows that some patients did withdraw from eculizumab treatment due to renal recovery; however, it was because the aHUS diagnosis was revised following the availability of additional clinical data and an alternative diagnosis was made. Consequently, the clinical improvement was not attributed to eculizumab and treatment was subsequently withdrawn. Therefore, no patients with aHUS discontinued due to renal recovery between 2016 and 2019; however, clinicians confirm that patients do discontinue for this reason (currently managed through the SETS study) and, depending on the SETS outcome, this may become more common in the future
- As discontinuation due to renal recovery is not a common clinical occurrence at present, and future rates are depend on the SETS study outcomes, this type of discontinuation is not included in the model base case; however, it is included in a scenario
  - In the scenario, the SETS protocol informs the proportion of patients who discontinue and at which time point. The SETS protocol states that the minimum treatment duration before patients can enrol is 6 months and that, after a preliminary assessment, approximately 60–70% of prevalent patients will be eligible to participate in the study.[70] Therefore, this scenario uses the minimum treatment duration for both arms (6 months) and assumes that 65% of patients on treatment at 6 months discontinue

    - Clinical opinion from the previous UK advisory board suggested that approximately 25% of patients would discontinue for this reason[20], which is considerably less than estimated from the SETS protocol. Thus, 25% is also tested in this scenario
- Patients who discontinue due to safety reasons, pregnancy, patient choice, death or other reasons (general discontinuation):
  - This could happen at any time point and is more in line with the discontinuation seen in the clinical trials

Based on the above, treatment discontinuation is complex with no generally applied current approach and a potential shift in future clinical practice is likely following results from the SETS study. While the treatment discontinuation data from the international clinical trials do help to inform general discontinuation (as detailed above), they do not fully reflect UK clinical practice, where management with eculizumab – particularly in terms of treatment initiation – is likely to differ.[24]

To capture expected treatment discontinuation in UK clinical practice as accurately as possible, the model captures the four elements of discontinuation separately using different sources and timings. These are then varied in sensitivity analyses and scenarios to ensure uncertainty around these inputs is captured.

B.3.3.1.1 Misdiagnosis

A simplified approach has been taken to capture the initial treatment period of patients before confirmed diagnosis. The drug and administration costs during the diagnosis period are calculated and applied as a one-off upfront cost within the model. This is expected to be the same in both treatment arms. These costs are uplifted to account for the fact that 100% of confirmed patients with aHUS 'start' the model. The base case for both treatment arms assumes that patients have a confirmed diagnosis in 1 month and that 17% of patients discontinue based on the NRCTC reports. This results in the costs being uplifted by 20% at the start of the model (1/(1–0.17) = 1.205).

B.3.3.1.2 General discontinuation

To capture patients who discontinued at any time point due to AEs, patient choice and so on, the data from the clinical trials are used. The patient-weighted data from the ravulizumab and eculizumab trials are pooled and fitted with parametric curves. Clinicians consulted did not expect discontinuation to differ between eculizumab and ravulizumab; therefore, pooling the data was considered appropriate for the base case.[24]

To maximize data, data from the long-term eculizumab trial (C11-003) were used for eculizumab and were pooled with the ravulizumab trials. Eleven patients within the weighted eculizumab data set did not enter the C11-003 follow-up trial; therefore, their time to treatment discontinuation (TTD) was based on their last treatment date in the parent study.

The pooled weighted patient-level data were fitted with parametric survival distributions: exponential, generalized gamma, Gompertz, log-normal, log-logistic and Weibull. Selecting the most appropriate distribution for the base case was done in accordance with NICE TSD 14.[71] Visual inspection and comparison of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to determine which distribution fitted the Kaplan–Meier (KM) data best during the observed period.

Table 31 presents the AIC and BIC fit statistics for each distribution. As can be seen, there is little difference in statistical fit between any of the curves. For the adult population, the data are relatively mature with a maximum follow-up of 7.6 years for eculizumab patients and 2.3 years for ravulizumab patients; however, the low patient numbers for the prior transplant and paediatric groups mean that individual events have a larger impact on the KM data, resulting in poorer curve fits.

For the non-transplant population, all the curves seem to fit the KM reasonably well, with some overestimation between 3 and 4 years. Weibull predicts the lowest proportion of patients still on treatment long-term, and log-normal predicts the highest proportion of patients still on treatment (Figure 17). For the prior transplant population, the shape of the KM curve (due to small patient numbers) meant that the

parametric curves did not fit well, underestimating the first 2 years and overestimating from 3 to 6 years (Figure 18). The curves fan out at 4 years, predicting very different proportions of patients on treatment by 20 years (0–15%). For the paediatric population, the shape of the KM curve (due to small patient numbers) meant that the parametric curves did not fit well, underestimating patients on treatment between 2 to 5 years (Figure 19). Visually, Gompertz and generalized gamma fit the data best but estimate that no patients are on treatment after 10 years, which is considered clinically implausible.

Clinical validation was sought to confirm the expectation of the proportion of patients on treatment over time; however, given the current complexity of treatment discontinuation, the changing of clinical practice and dependency on patient circumstances, clinicians could not provide estimates to use for validation. Available UK registry data provide some information on treatment discontinuation rates for patients receiving eculizumab in practice but do not provide longer-term data than the trials (n=82 total; n=15 remaining at 6 years). The UK registry data show that most patients who discontinue do so early on; however, it should be noted that these data include all types of discontinuation and not just general discontinuation.

Given the complexity of treatment discontinuation and the lack of data and clinical uncertainty associated with long-term outcomes, the base case choice is primarily driven by visual fit to the non-transplant data (where the most information exists), the implied assumption of the hazard from the curve selected with other curves tested in scenario analysis and the expectation that some patients will remain on treatment in the long term (>10 years) in all populations. The exponential curve has been selected as the base case for all groups; this curve sits between the lower and upper predicted curves and assumes a constant rate of treatment discontinuation over time. This assumption seems reasonable given that it represents general reasons to discontinue treatment and can happen at any time point. All other curves are tested in scenario analysis.

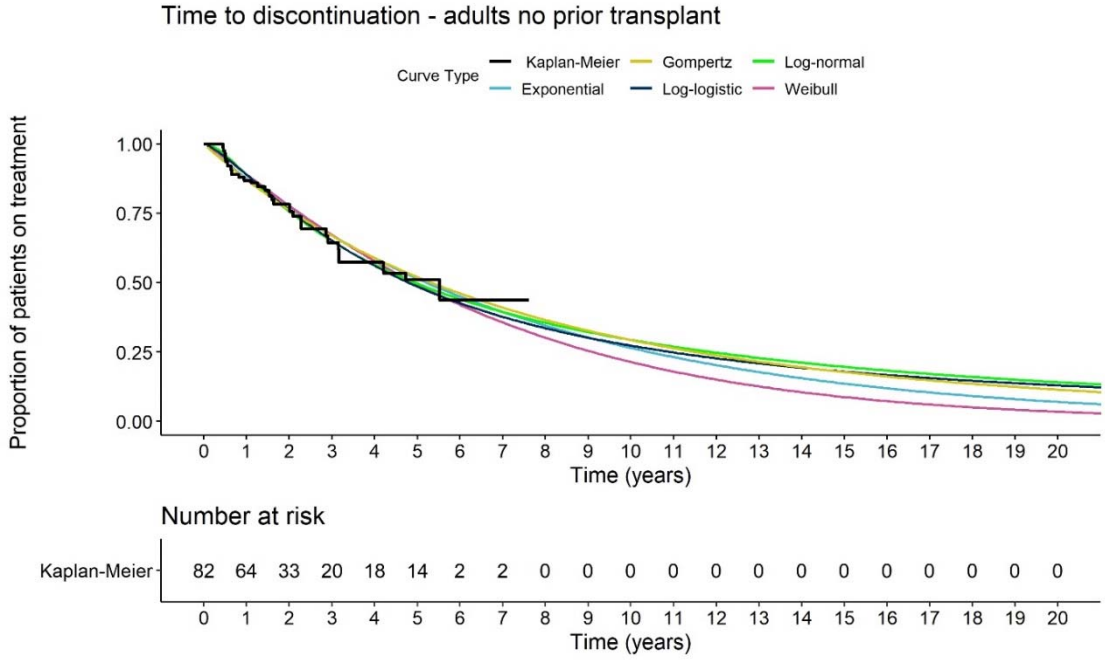
Given that the same curves are used for both treatment arms, the choice of curve does not have much influence on the model results.

Table 31: TTD: AIC and BIC – pooled C11-003 and 311/312

Distribution	Adults (non-transplant)		Adults (prior transplant)		Children	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	**280.98**	**283.38**	**78.77**	**79.87**	**102.02**	103.49
Generalized gamma	NA	NA	**82.32**	85.59	**103.34**	107.74
Gompertz	**282.93**	287.75	**80.67**	82.85	**100.40**	**103.33**
Log-logistic	**280.82**	285.63	**80.13**	82.31	**103.31**	106.24
Log-normal	**278.75**	283.56	**81.32**	83.50	**104.59**	107.52
Weibull	**282.44**	287.26	**80.34**	82.52	**102.35**	105.29

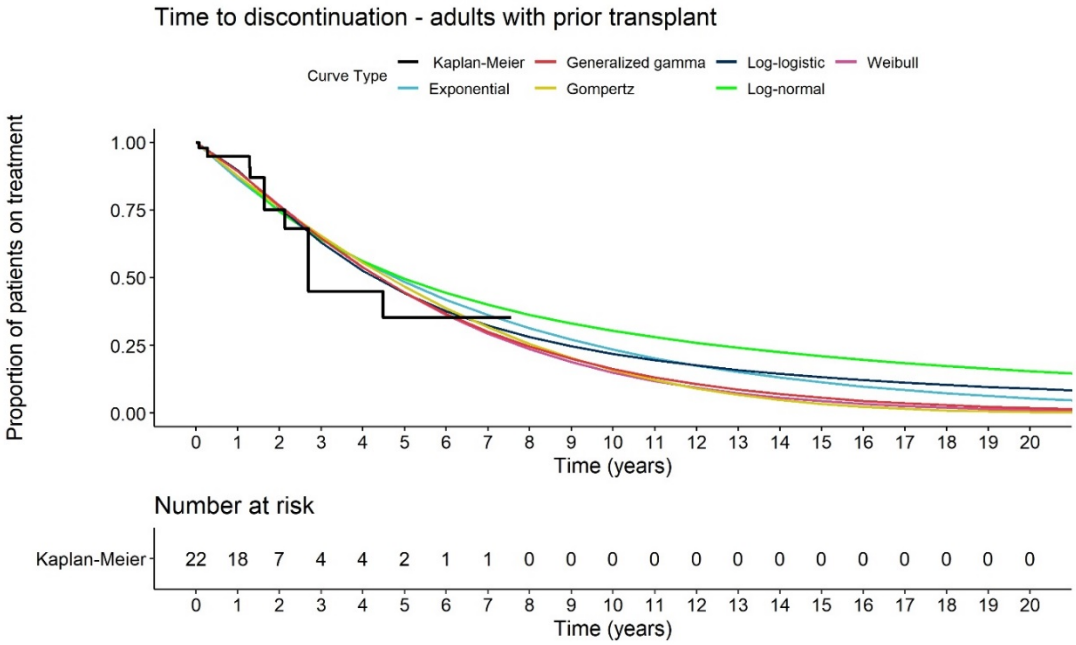
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NA, not applicable; TTD, time to treatment discontinuation.
Notes: Generalized gamma did not converge for the non-transplant adult population.
Bold and underlined represents the best-fitting curves. **Bold** represents curves with a similar goodness of fit to the best-fitting curve (AIC within 5).

Figure 17: TTD parametric curves – pooled C11-003 and 311 (adults – non-transplant)



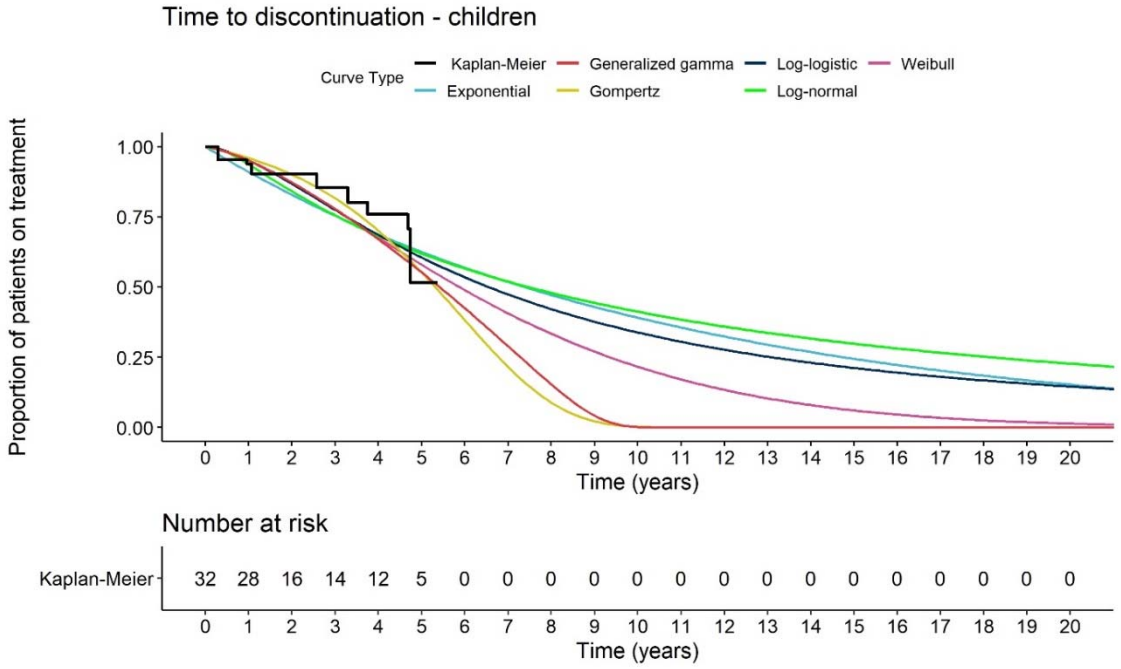
Key: Exp, exponential; gomp, Gompertz; log-log, log-logistic; log-norm, log-normal; KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Figure 18: TTD parametric curves – pooled C11-003 and 311 (adults – prior transplant)



Key: Exp, exponential; gen gamma; generalized gamma; gomp, Gompertz; log-log, log-logistic; log-norm, log-normal; KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Figure 19: TTD parametric curves – pooled C11-003 and 312 (children)

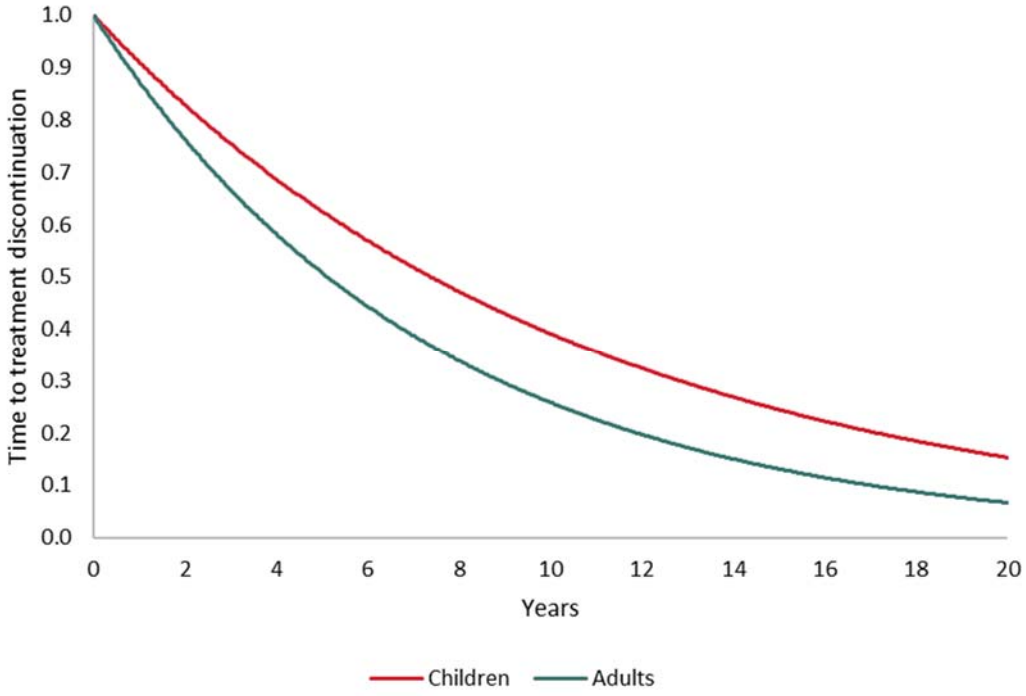


Key: Exp, exponential; gen gamma; generalized gamma; gomp, Gompertz; log-log, log-logistic; log-norm, log-normal; KM, Kaplan–Meier; TTD, time to treatment discontinuation.

For the adult population, the selected curves are weighted based on how many patients have received a prior transplant (see Appendix N). The final curves chosen to represent treatment discontinuation for adults and children are presented in Figure 20.

The global aHUS registry is an alternative source of treatment discontinuation data, and these are used in a scenario analysis. The global aHUS registry was initiated in April 2012 and aimed to assess the long-term effects of aHUS and to collect and evaluate the safety and effectiveness of using eculizumab to treat patients with aHUS.[31] The registry covers all types of discontinuation and so, when the associated data are applied in the scenario analysis, all other types of discontinuation described above are excluded. Treatment discontinuation data from the April 2020 data cut for the UK population were used and fitted with parametric curves as above. Details of these data are provided in the Appendix O.2.

Figure 20: Final TTD parametric curves



Key: TTD, time to treatment discontinuation.

B.3.3.1.3 No renal response

In UK clinical practice, patients on eculizumab with no renal response would usually discontinue treatment after 3–4 months[24]; according to the NRCTC reports, this occurs in around 23% of patients who are initiated on therapy.[19, 68, 69] However, according to the SmPC, ravulizumab should be given for a minimum of 6 months to resolve TMA manifestations (with the exception of misdiagnosis).[1] Therefore, for the model base case, it is assumed that ravulizumab patients would not discontinue due to no renal response for a minimum of 6 months, in line with the SmPC. As clinicians felt that in UK clinical practice it is unlikely that patients with no renal recovery would receive ravulizumab for the full 6 months, the impact of discontinuation due to non-response at the same time point as eculizumab is tested in a scenario analysis. In the model, eculizumab patients experiencing no renal response are discontinued at 3.5 months. The remaining patients on treatment continue to follow the treatment discontinuation rate estimated from the extrapolated curves from general discontinuation.

B.3.3.1.4 Summary

Table 32 summarizes treatment discontinuation timings and expected % of patients.

Table 32: Treatment discontinuation summary

Reason for discontinuing treatment	Eculizumab		Ravulizumab	
	Timing	% of patients	Timing	% of patients
Different diagnosis	1 month	17% (NRCTC)[19, 68, 69]	1 month	As per eculizumab
General	Any time (continuous)	Pooled weighted ITC data extrapolated	Any time (continuous)	Pooled weighted ITC data extrapolated
No renal recovery	3.5 months (mid-point between 3–4 months)[24]	23% (NRCTC)[19, 68, 69]	6 months (SmPC) [1] (3.5 months in scenario analysis)	As per eculizumab

Renal recovery	Not applied in base case (6 months in scenario analysis)	Not applied in base case (65% and 25% in scenario analysis)	Not applied in base case (6 months in scenario analysis)	Not applied in base case (65% and 25% in scenario analysis)
Key: ITC, indirect treatment comparison; SmPC, summary of product characteristics; NRCTC, National Renal Complement Therapeutics Centre.				

B.3.3.2 Relapse and treatment reinitiation

In the aHUS registry, 82 patients from the UK were included and were treated with eculizumab (56 adults and 26 children). Of the 82 patients, 40 patients discontinued (26 [46.4%] adults and 14 [53.8%] children). Eighteen patients subsequently relapsed and reinitiated eculizumab treatment (11 [42.3%] adults and 7 [50.0%] children).[72]

A similar rate was reported in the long-term eculizumab study C11-003, as reported in Menne et al. (2019), whereby 42 patients discontinued eculizumab treatment.[63] Of those, 21 (50.0%) patients relapsed and resumed eculizumab treatment. Literature sources also show similar rates of TMA recurrence after discontinuing eculizumab, ranging from 20% to 67%.[73-80]

Therefore, in the model we have assumed that 42.3% of adults and 50.0% of children relapse and all patients who relapse reinitiate treatment, as per the aHUS registry. The rate used for children is only used until the mean age of the population reaches 18; after this time, the adult rate is used for the remaining time horizon. This is assumed for both eculizumab and ravulizumab.

B.3.3.3 Safety

The AEs associated with ravulizumab and eculizumab are expected to be similar for patients with aHUS and, therefore, have a small impact on the model results. Both drugs had similar safety profiles based on clinical trial results, and clinicians agree that they would expect the safety profiles of the two treatments to be similar.[24] Four deaths were observed in the ravulizumab trial, but they were not deemed to be drug-related by the investigators. Furthermore, the patients who died were considered severely ill before entering the trial and clinical expert opinion is that, in practice, these patients would not have been eligible for complement-inhibitor treatment in the UK (see Section B.2.10.3).[24] The head-to-head PNH trial also demonstrated similar

safety profiles for eculizumab and ravulizumab, which is unlikely to differ for patients with aHUS.[49, 50] Therefore, AEs are not considered in the model.

B.3.4. Measurement and valuation of health effects

As discussed in Section B.3.2, the primary analysis assumes equivalent efficacy between ravulizumab and eculizumab, and therefore, does not consider QALY differences between treatment arms. In the secondary analysis looking at differential efficacy, health-states are measured in QALYs. Further details of the utilities used to measure the health states are described in Appendix N.2.

B.3.4.1 Health-related quality of life data from clinical trials

EQ-5D-3L data were collected in some of the ravulizumab and eculizumab trials, mainly for the adult population. The trials that only recruited paediatric patients did not collect any EQ-5D data, but some EQ-5D paediatric data were collected within the C08-003 trial. The frequency of the EQ-5D data collection varied by trial, but all trials had data for the start and end of the initial evaluation phase (26 weeks) with some data beyond 26 weeks.

Responses to the EQ-5D-3L collected in clinical studies were scored using a time-trade off value set for the UK.[81] Patients with missing data from any of the five domains were removed from the analysis in addition to patients who had a missing or unknown CKD stage at the time of EQ-5D questionnaire.

UK time-trade off summaries were stratified by baseline treatment, baseline CKD stage and post-baseline treatment and post-baseline CKD stage (presented in Table 33). While observation numbers are limited, it can be seen that patients receiving ravulizumab had lower utilities at baseline (0.39 vs 0.63) and therefore showed a greater improvement in utilities post-baseline (0.39 to 0.81 for patients receiving ravulizumab vs 0.63 to 0.86 for patients receiving eculizumab).

Mixed-effects models were derived to estimate utilities adjusted for health states and for repeated measures within subjects. The full methods and results of the exploratory analysis and mixed-effects modelling are shown in Appendix M.

Table 33: EQ-5D estimates from clinical studies descriptive summaries

CKD stage	Treatment	Baseline			Post-baseline		
		N observations	N patients	Mean (95% CI)	N observations	N patients	Mean (95% CI)
0–2	Eculizumab	2	2	0.84 (0.54, 1.15)	208	21	0.94 (0.92, 0.95)
	Ravulizumab	3	3	0.35 (-0.09, 0.78)	85	22	0.89 (0.84, 0.93)
	Pooled	5	5	0.55 (0.20, 0.90)	293	43	0.92 (0.91, 0.94)
3	Eculizumab	14	14	0.70 (0.50, 0.91)	395	44	0.88 (0.87, 0.90)
	Ravulizumab	3	3	0.56 (0.20, 0.93)	50	23	0.85 (0.80, 0.91)
	Pooled	17	17	0.68 (0.50, 0.86)	445	67	0.88 (0.86, 0.90)
4	Eculizumab	14	14	0.73 (0.61, 0.85)	308	31	0.80 (0.78, 0.82)
	Ravulizumab	9	9	0.65 (0.40, 0.90)	29	17	0.77 (0.66, 0.88)
	Pooled	23	23	0.70 (0.58, 0.82)	337	48	0.80 (0.78, 0.82)
5	Eculizumab	32	32	0.55 (0.40, 0.69)	154	27	0.78 (0.74, 0.82)
	Ravulizumab	34	34	0.31 (0.14, 0.48)	110	35	0.74 (0.68, 0.80)
	Pooled	66	66	0.42 (0.31, 0.54)	264	62	0.76 (0.73, 0.79)
Overall	Eculizumab	62	62	0.63 (0.54, 0.73)	1065	71	0.86 (0.84, 0.87)
	Ravulizumab	49	49	0.39 (0.25, 0.52)	274	54	0.81 (0.78, 0.84)
	Pooled	111	111	0.52 (0.44, 0.61)	1,339	125	0.85 (0.83, 0.86)

Key: CI, confidence interval; CKD, chronic kidney disease; FAS, Full Analysis Set; ITT, intention-to-treat.
Note: This table includes baseline and post-baseline data for prior transplant and no transplant patients from aHUS-311 (FAS), C08-002 (ITT), C08-003 (ITT) and C10-003 (ITT). Utility records were excluded for which a CKD stage was missing or unknown at time of baseline.

Table 34 presents the final mixed-effects model after selecting the most appropriate regression model. Baseline utility, CKD stage, and the expected decreases in utility outcome that occur as CKD stages increase all have a significant effect on post-baseline utility. In this model, treatment does not have a significant effect on utility; however, the direction of effect was 0.05 (p=0.132) in favour of ravulizumab when accounting for differences in baseline utility (see Appendix M).

Table 34: Summary of final fitted mixed-effects model

Coefficient	Parameter value	SE	p-value
(Intercept)	0.78	0.03	<0.001
Baseline utility	0.24	0.04	<0.001
CKD Stage 3	-0.05	0.02	0.006
CKD Stage 4	-0.15	0.02	<0.001
CKD Stage 5	-0.21	0.02	<0.001
Baseline utility			<0.001
CKD stage			<0.001
Model fit diagnostics			
AIC	-1,041.45		
BIC	-1,005.62		
Key: AIK, Akaike information criterion; BIC, Bayesian information criterion; CKD, chronic kidney disease; SE, standard error.			

B.3.4.2 Mapping

EQ-5D values were collected directly from the clinical trials; therefore, no mapping was required.

B.3.4.3 Health-related quality of life studies

A systematic literature review was conducted to identify all relevant utility studies for the treatment of patients with aHUS. Of the 10 studies identified in the economic systematic review (see Section B.3.1 and Figure 15), four reported HRQL outcomes. The process of study identification, search strategies and a description of the included utility studies are presented in Appendix H.

HRQL was not well reported among the included studies. All four of the publications discussed HRQL data from the ravulizumab or eculizumab trials. Details of these descriptions are provided in Appendix H.

The previous NICE aHUS submission (HST1) used EQ-5D utility values estimated from the C08-002 and C08-003 trials.[16] EQ-5D values for CKD 0–2, CKD 3–4 and ESRD at Day 364 were assumed to reflect the utility scores for patients receiving eculizumab. The difference between all scores at baseline and at the median treatment duration of 62 weeks was estimated to be 0.208. This value was used to estimate the difference in HRQL for patients receiving standard care versus eculizumab and was applied as a disutility to all standard care CKD states. The utility within the transplant tunnel state was assumed to be the same as the utility for the standard care CKD 3–4 state (value = 0.662).

The van de Brand et al. (2017) study used utility values from a systematic review and meta-analysis of utility-based quality of life in CKD treatments for dialysis and patients living with transplant.[82] A utility reduction of 5.5% on average (ranging between 1 and 11%), due to the recurrence of aHUS without suffering graft loss, was based on expert opinion.

Table 35 summarizes the utility studies identified in the review that were not based on the clinical trials.

Table 35: HRQL studies identified in the SLR

Study	Year	Utility measure	Mean utility
Tappenden 2013, NICE 2015[16]	2013	EQ-5D	Eculizumab: CKD 0–2 = 1, CKD 3–4 = 0.87, ESRD = 0.867 Transplant = 0.662 Standard care: CKD 0–2 = 0.792, CKD 3–4 = 0.662, ESRD = 0.659 Transplant = 0.662
Van de Brand[52]	2017	Systematic review[82] and expert opinion	5.5% utility reduction due to aHUS recurrence

Key: aHUS, atypical haemolytic uremic syndrome; CKD, chronic kidney disease; ESRD, end-stage renal disease; HRQL, health-related quality of life; NICE, National Institute for Health and Care Excellence; SLR, systemic literature review.

B.3.4.4 Adverse reactions

As discussed in Section B.3.3, no differences in AEs associated with ravulizumab and eculizumab are expected. Therefore, no disutilities associated with adverse reactions have been included in the economic model.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Full details of the HRQL data used in the scenario analysis are presented in Appendix N.2.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In line with the NICE reference case, the perspective on costs in all cost-effectiveness analyses is that of the NHS and PSS in England. A systemic literature review for healthcare resource use and cost data is reported in Appendix I. Three publications reported two studies on direct and indirect costs. One study reported the impact of early versus late eculizumab initiation[83, 84] and the other reported a US-based cost-consequence model investigating the productivity loss of treating patients with aHUS with eculizumab or ravulizumab.[85] These studies report US costs and do not provide any useful inputs for this model structure.

Table 36 summarizes the associated health care resource use costs. Further details of how these costs have been calculated are provided in the sections below.

Table 36: Healthcare resource costs

Health state	Cost	Source/justification
Drug acquisition[a]	First year: Ravulizumab: [redacted] (adults), [redacted] (children) Eculizumab: £352,800 (adults), £168,407 (children)	MIMS[86] Costs are based on patient weight distribution dosing frequency as per their SmPC[1, 25]
Administration costs[b]	Ravulizumab: Average £208 per dose Eculizumab: £195	PSSRU (2019)[87] Combination of associated nurse specialist (£113) and pharma specialist (£57). Infusion times as per SmPC with additional 1-hour nurse observation time[1, 25]
Meningococcal vaccine	£290	Hampstead Health Pharmacy[88] Combination of MenACWY (£60) and MenB vaccine (£115) (see Table 41 for further details)
Treatment monitoring	£69.70 (first year per 2-week cycle) £69.57 (after first year per 2-week cycle)	NRCTC[89] NHS ref 18/1[90] NHS 2015.[91]
Discontinuation cost	£98.87 (per 2-week cycle)	SETS protocol[70] NHS ref 18/1[90] NHS 2015[91]
Relapse cost	£1,272.84 (per 2-week cycle)	Silver 2017[92], cost of diagnosis of acute kidney injury, inflation adjusted
Health state costs (per 2-week cycle)		
CKD 0–2	£17.35	Costs are calculated based on annual hospital care costs in the absence of diabetes and cardiovascular complications (Kent et al. [2015])[58]
CKD 3a–3b	£17.35	
CKD 4	£16.92	
CKD 5/ESRD	£22.61	
Transplant	£1,059.38	
Transplant success	£49.43	

Key: CKD, chronic kidney disease; ESRD, end-stage renal disease; MIMS, Monthly Index of Medical Specialities; NRCTC, National Renal Complement Therapeutics Centre; PSSRU, Personal Social Services Resource Unit; SmPC, summary of product characteristics.
Note: [a] Drug costs shown exclude VAT, are based on PAS price for ravulizumab and list price for eculizumab (no PAS applies) and assume no discontinuation. [b] Administration costs are only applied to patients who do not receive homecare – [redacted]% of patients (funded by Alexion).

B.3.5.1 Intervention and comparator costs and resource use

B.3.5.1.1 Drug acquisition costs

Table 37 summarizes the drug unit size, pack size and associated cost for ravulizumab and eculizumab. A description of the cost per pack, source and the proposed patient access scheme (PAS) is included.

Table 37: Drug unit size, pack size and pack cost

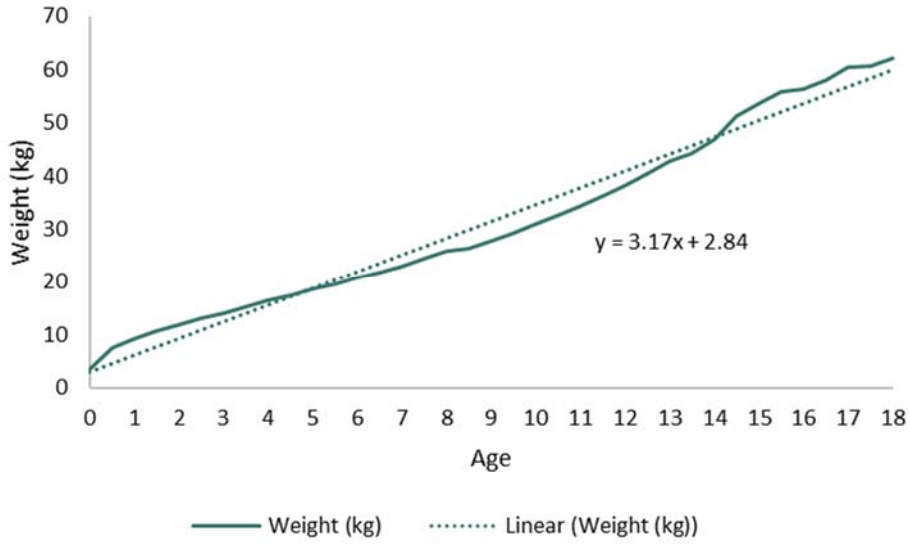
Treatment	Unit size	Pack size	Cost per pack	Source
Ravulizumab	300 mg	1	£4,533 (£[redacted] with PAS)	Alexion pricing[93]
	1,100 mg	1	[redacted] (£[redacted] with PAS)	Alexion pricing
Eculizumab	300 mg	1	£3,150	MIMS (2019)[86]
Key: MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme. **Note:** A PAS of [redacted] was applied to ravulizumab vials.				

The dosing schedules for eculizumab and ravulizumab are presented in Section B.3.2, Table 30. To accurately account for the variation in patient weights, the per-cycle treatment cost for eculizumab and ravulizumab uses the weight distribution from the associated clinical trial data to calculate the average cost per cycle. Accurately capturing the patient weight distribution has been considered particularly important due to the large variation in patient weights within the patient population; this is due to both the paediatric population and adults being considered in the ITT population. The weight distribution was used to calculate the average costs of ravulizumab treatment and eculizumab treatment.

The changing weight of paediatric patients is accounted for within the model. The average weight of children in the UK per age, taken from the Royal College of Paediatrics and Child Health (RCPCH) UK-World Health Organization (WHO) growth charts, was used to calculate the average growth rate per 6 months for paediatric patients less than 18 years old.[94, 95] This was estimated as an increase of 3.2 kg per 6 months, assuming a linear increase (see Figure 21), and was applied to the baseline weight distribution over time. To ensure that paediatric patients are not

heavier than the adult starting population when they reach adulthood, their weight is assumed to remain the same when either the patient turns 18 (adult patient weights remain consistent over the model time horizon) or the mean overall weight matches the mean overall weight of the adult population.

Figure 21: RCPCH UK-WHO growth charts per age[94, 95]



Key: RCPCH, Royal College of Paediatrics and Child Health; WHO, World Health Organization.

The cost of the first year of treatment for ravulizumab and eculizumab in the base case is presented in Table 38. Due to the different dosing schedules, the average treatment cost of ravulizumab for the first year of treatment is [redacted] and [redacted] cheaper than eculizumab for adults and children, respectively.

Table 38: Cost of the first year of treatment

Treatment	Ravulizumab	Eculizumab
First year – adults	[redacted]	£352,800
First year – children	[redacted]	£168,407

B.3.5.1.2 Administration costs

Ravulizumab and eculizumab are administered intravenously; eculizumab is administered via a 25–45-minute infusion[25] but the ravulizumab infusion time varies

depending on age and weight band (see Table 39). The model uses a 15-minute preparation time for each administration for both ravulizumab and eculizumab.

Table 39: Infusion times (hours) for ravulizumab (100 mg/mL formulation)

Body weight (kg)	Induction		Maintenance	
	Prep time	Infusion time	Prep time	Infusion time
≥ 10 to < 20	0.25	0.8	0.25	0.8
≥ 20 to < 30	0.25	0.6	0.25	1.3
≥ 30 to < 40	0.25	0.5	0.25	1.1
≥ 40 to < 60	0.25	0.8	0.25	0.9
≥ 60 to < 100	0.25	0.6	0.25	0.7
≥ 100	0.25	0.4	0.25	0.5

The costs of specialist nurse and pharmacist time have been incorporated in the administration costs for both eculizumab and ravulizumab. Associated PSS Resource Unit costs have been used to inform the overall cost.[87] This includes a combination of associated nurse specialist (£113) and pharmacist specialist (£57) time. An additional observation time of 1 hour has been assumed in the administration cost calculation and is included in the nurse time allocation. The total administration cost per dose is summarized in Table 40.

Table 40: Total administration cost per dose (100 mg/mL formulation)

Body weight (kg)	Ravulizumab		Eculizumab
	Induction	Maintenance	
≥ 10 to < 20	£218	£218	£195
≥ 20 to < 30	£195	£274	
≥ 30 to < 40	£184	£252	
≥ 40 to < 60	£218	£229	
≥ 60 to < 100	£195	£206	
≥ 100	£172	£184	

After a certain time, some patients responding well to treatment will receive their administrations at home through Alexion's homecare programme. Most patients will receive homecare after approximately their fifth eculizumab dose. Based on personal communication with NRCTC, [redacted] patients currently on eculizumab

treatment are receiving homecare (data on file). Therefore, in the model, the base case assumes that [redacted]% of patients receive homecare after their fifth dose. It is assumed that [redacted]% of patients on ravulizumab also receive homecare, but this will be after the initial loading dose and two maintenance doses. Administration costs for patients receiving homecare are not included in the model as these costs are covered by Alexion.

B.3.5.1.3 Meningococcal vaccine and prophylactic antibiotics

Ravulizumab and eculizumab administration, and the associated complement system inhibition, may increase the risk of meningococcal infection. The SmPCs for eculizumab and ravulizumab suggest that all patients must be vaccinated against meningococcal infections at least 2 weeks before receiving treatment, unless the risk of delaying treatment outweighs the risks of developing a meningococcal infection.[1, 25] Costs and dosing for the two necessary vaccines, MenACWY and MenB, were derived from Hampstead Health Pharmacy.[88] Additionally, the MenACWY SmPC indicates that a booster vaccination is available up to 5 years after vaccination[96]; therefore, in the model, MenACWY vaccination is given every 5 years for patients receiving complement-inhibitor treatment. Given that no specific advice was identified for MenB, the same was assumed and confirmed by clinical opinion. Table 41 provides an overview of the dosing regimens required.

Table 41: Meningococcal vaccination cost and dose frequency

Vaccine	Cost per dose	Number of doses required	Source	Frequency of booster doses	Source
MenACWY vaccine	£60	1	Hampstead Health Pharmacy[88]	Every 5 years	MenACWY SmPC[96]
MenB vaccine	£115	2		Every 5 years (one dose only)	Assumption

Key: SmPC, summary of product characteristics.
Note: As the vaccination history is assumed unknown for treatment experienced patients, a booster vaccine is given at the start of model and every 5 years thereafter.

The costs provided include the costs of administration and consultation. These costs are applied to both treatment arms.

The aHUS National Service recommends continuous prophylactic antibiotics, specifically penicillin, for all eculizumab-treated patients and the same is expected to apply to ravulizumab. The drug cost was derived from the drugs and pharmaceutical electronic market information tool (eMIT).[97] Multiple price options were presented at differing doses; therefore, it was assumed that the pack providing the cheapest cost per mg would be used (see Table 42).

Table 42: Penicillin cost per pack

Description	Cost per pack
Phenoxymethylpenicillin 250 mg tablets/pack size 28 (DEA229)	£0.36

It was assumed that prophylactic penicillin would be given at a dose of 500 mg, twice daily. This results in a cost per cycle of £0.72. The costs were applied to both treatment arms.

B.3.5.1.4 Treatment monitoring

According to the NRCTC, testing for evidence of the complement blockade, by CH100, AH100 (or CH50/AH500) and soluble C5b-9, is recommended during follow-up while patients are on eculizumab. These are recommended every 3 months in the first year and annually thereafter. Additionally, monthly blood tests are recommended.[89] It is assumed that these tests take place at an outpatient consultation. Treatment monitoring is not expected to differ for ravulizumab; therefore, treatment monitoring costs are assumed the same for both treatments.

Costs for treatment monitoring have been sourced from NHS reference costs 18/19[90] or NHS preoperative costs 2016[91] uplifted to 2019 costs. The total costs per model cycle are £69.97 for the first year and £69.85 thereafter.

Table 43 summarizes the treatment monitoring frequencies and unit costs used in the model.

Table 43: Summary of treatment monitoring costs

Resource use	Frequency	Cost	Source
Outpatient consultant	Monthly	£131.01	NHS ref 18/19 - Total outpatient attendances 822 Chemical Pathology[90]
Evidence of blockade (CH100, AH100 or CH50/AH500) and soluble C5b-9)	Every 3 months for the first year and annually thereafter	£1.10	NHS ref 18/19 - DAPS04 - Clinical Biochemistry[90]
Renal function	Monthly	£1.10	NHS ref 18/19 - DAPS04 - Clinical biochemistry[90]
Full blood count		£2.79	NHS ref 18/19 - DAPS05 - Haematology[90]
Lactate dehydrogenase		£2.79	NHS ref 18/19 - DAPS05 - Haematology[90]
Haptoglobin		£2.79	NHS ref 18/19 - DAPS05 - Haematology[90]
Urinalysis		£4.33	NHS 2015. Preoperative tests, Appendix M, Table 2. Uplifted to 2019 costs[91]
Urine protein/creatinine ratio		£6.36	NHS 2015. Preoperative tests, Appendix M, Table 3. Uplifted to 2019 costs[91]

B.3.5.1.5 Discontinuation costs

The outcomes of patients who discontinue treatment are being assessed in the ongoing SETS trial. The SETS study is a UK multicentre, open-label, prospective, single-arm study of the safety and impact of eculizumab withdrawal in patients with aHUS.[62] Outcomes from SETS will inform future practice which will likely be in line with SETS criteria (see Section B.1.3.2). Therefore, costs to inform discontinuation monitoring are based on the SETS protocol. It is likely that monitoring will be less intensive compared with the SETS study in UK practice. However, these costs are used as an upper bound of the costs incurred by the NHS.

Patients are assessed regularly for evidence of disease relapse for the duration of the 2-year study period. Patients are reviewed weekly for the first month, then alternate weeks until Week 6 and then monthly until the end of the 2 years.[70] Not all tests are conducted at every visit (see Table 44). In addition to frequent visits, patients are also expected to conduct regular self-monitored urinalysis. These are

performed daily by the patient or carer for the first month, then three times per week for the duration of the study. The SETS study includes patients with Stages 0–3 CKD, although clinical opinion suggests that patients with Stage 4 CKD will be monitored like those with other stages of CKD therefore the same monitoring costs have been used. However, patients with Stage 5 CKD would be monitored like patients on dialysis; therefore, specific health state costs covering dialysis are used for this health state (see Section on CKD stage costs).

Table 44: Discontinuation monitoring (SETS protocol)

Resource	Frequency	Unit cost	Cost source
General (temperature, blood pressure, pulse, concomitant medication review)	Weekly for the first month Bi-weekly until 6 months, then monthly	£131.01	NHS ref 18/19 - Total outpatient attendances 822 Chemical Pathology[90]
Renal function (eGFR)		£1.10	NHS ref 18/19 - DAPS04 - Clinical Biochemistry[90]
Urinalysis and diary review		£4.57	NHS 2015. Preoperative tests, Appendix M, Table 2. Uplifted to 2019 costs[91]
Haemolysis markers		£2.79	NHS ref 18/19 - DAPS05 - Haematology[90]
Electrolyte profile		£1.10	NHS ref 18/19 - DAPS04 - Clinical biochemistry[90]
Liver function		£1.10	NHS ref 18/19 - DAPS04 - Clinical biochemistry[90]
Self-monitored urinalysis	Daily for the first month, then three times per week during the 2-year period	£4.08	NHS 2015. Preoperative tests, Appendix M, Table 1. Uplifted to 2019 costs[91]
Biomarkers and complement activation samples	11 times during the 2-year period	£1.10	NHS ref 18/19 - DAPS04 - Clinical biochemistry[90]
Haptoglobin and blood film	Seven times during the 2-year period	£2.79	NHS ref 18/19 - DAPS05 - Haematology[90]
Urine protein/creatinine ratio		£6.72	NHS 2015. Preoperative tests, Appendix M, Table 3. Uplifted to 2019 costs[91]
Physical examination	Twice in the 2-year period	£62.11	NHS ref 18/19 - Total outpatient attendances 304 Clinical Physiology[90]
Key: eGFR, estimated glomerular filtration rate.			

Given the different frequencies and complexity of the visits, the total costs over the 2-year period are calculated and applied as an average 2-weekly cost in each model cycle. This results in a total cost of £5,159 over the 2 years and a £99 average cost per 2 weeks. The impact of this simplification is expected to be very small as these costs represent only 0.4% and 0.3% of the total costs of the ravulizumab and eculizumab arms, respectively, and there will only be a minor loss of accuracy from discounting.

B.3.5.1.6 Costs of relapse

A one-off cost is applied at the time of relapse. Fakhouri et al. (2017) report that among patients who experienced relapse 'all but one patient presented with mechanical haemolysis and acute kidney injury'.[75] It is therefore assumed that a patient experiencing acute kidney injury on relapse would require increased medical visits at a minimum and, in more severe cases, they may require dialysis. Given the lack of data on the medical resource use and costs of relapsed patients with aHUS, published literature on the economic burden of acute kidney injury was used. Silver et al. (2017) reported that the inpatient costs related to acute kidney injury were approximately £1,100 per episode[92]; therefore, the average cost of a patient relapsing is £1,273 after inflation to 2019 costs.

B.3.5.1.7 Reinitiate treatment

Patients who reinitiate treatment due to relapse incur drug, administration, meningococcal vaccine and antibiotics costs; it is assumed that these patients will remain on lifelong treatment. Although many factors may cause patients to discontinue treatment again, due to lack of data and for simplicity, this assumption has been carried forward.

The costs incurred by patients are applied using a pay-off approach, where the lifetime cost per patent is calculated and applied upfront to each patient entering the reinitiation health state. The total cost per patient involves numerous factors: the timing of reinitiation, patient weight and cost DR. The mean treatment duration is calculated based on the treatment-specific mean survival at each time point predicted by the model. For example, at the start of the model, the average survival for adults receiving ravulizumab is 31.2 years. This value is then used to look up the

total cost per patient of receiving ravulizumab treatment for 31.2 years. These costs are calculated at each time point. For the paediatric population, the weight distribution change is accounted for and updated per time point to accurately reflect the weight distribution of patients who relapse at each time point.

To calculate the DR between two discrete time points, the following formulae was used. First the instantaneous discount rate (iDR) was calculated from the annual DR:

$$iDR = \ln(1 + DR)$$

Using the iDR, the continuous discount rate between two discrete time points could then be calculated:

$$Discounted\ number\ of\ years = \frac{(t_{new\ event} - iDR)^e - (t_{previous\ event} - iDR)^e}{-iDR}$$

$t_{new\ event}$ was calculated as the current time point (i.e. time of reinitiation) plus the mean survival at time of relapse and $t_{previous\ event}$ was the current time point at time of reinitiation.

The continuous DR per time point was then applied to the total cost to produce the total discounted cost per patient per time of treatment reinitiation.

B.3.5.2 Health state unit costs and resource use

B.3.5.2.1 *CKD stage costs*

Patients with aHUS can require hospitalization, and the costs can vary by CKD stage. Therefore, specific costs for hospitalizing patients with aHUS are applied separately per CKD stage.

To identify CKD medical management costs attributable to aHUS, a targeted literature search was conducted. Specifically, a PubMed search was performed in June 2019 based on the Medical Subject Heading ‘Renal Insufficiency, Chronic’, subheading ‘economics’ and key term ‘United Kingdom’. Results were identified and reviewed for relevant information on costs from the UK perspective. Titles and abstracts were reviewed for relevance, with a preference for studies after 2010. Of the evidence identified via the targeted search, three studies were considered for

estimates of the UK costs for managing CKD: Kent et al. (2015), Li et al. (2015) and Kerr et al. (2012).[58, 98, 99]

Kent et al. estimated the cost of hospital care using a regression analysis of individual data from more than 7,000 patients with CKD. The reported hospital cost model allows the annual hospital care costs (in UK prices) to be estimated for a patient with CKD.[58] Li et al. analysed a Hospital Episodes Statistics dataset that was linked to the UK Renal Registry for patients who started renal replacement therapy for ESRD in England between 2003 and 2006. The paper explores the hospital inpatient and outpatient costs over a number of years, among both dialysis and transplant patients.[98] Kerr et al. estimated the annual cost to the NHS in England of Stages 3–5 CKD, including ESRD.[99]

Kent et al. is the most recent source and provided a uniform source for costs for CKD stage, dialysis and transplant. Therefore, the estimate by Kent et al. of the cost of hospital care for patients with CKD is used to parametrize CKD 0 to CKD 5 (not on dialysis) costs. For ESRD (CKD 5, on dialysis), it was assumed that over a 2-week ESRD period, patients would require dialysis.

The total costs per CKD stage are inflated to 2019 costs and transformed to 2-weekly costs to match the model cycle length (Table 45). Due to assuming equal efficacy in the base case, these health state costs only account for 0.017% of the total absolute cost differences between treatment arms (this is due to different treatment discontinuation timings).

Table 45: CKD stage hospital costs

CKD stage	2-weekly cost	Source
0–2	£17.35	Kent et al. (2015)[58] Inflated to 2019 costs
3a–3b	£17.35	
4	£16.92	
5/ESRD	£22.61	
Key: CKD, chronic kidney disease; ESRD, end-stage renal disease.		

B.3.5.2.2 *Kidney transplant costs*

For patients who undergo kidney transplant, the cost of the 2-week period in which the transplant is received is required in addition to costs in later periods (e.g. for monitoring, complications and drugs such as immunosuppressants). These costs were taken from Kent et al., who reported a first-year transplant cost of £24,602 (2011) and a maintenance cost of £1,148 per annum thereafter. These costs were inflated to 2019 values and transformed to 2-weekly costs for the model, resulting in a cost of £1,059.38 for transplant and £49.43 for maintenance.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of all base case parameters and distributions are provided in Appendix Q.

B.3.6.2 Assumptions

As aHUS is an ultra-rare disease with very few patients, a head-to-head trial was not considered feasible by the EMA.[39] The lack of head-to-head data and sparsity of literature in general means that the model includes some assumptions. Where possible, Alexion has sought information from available registries, longer-term eculizumab data and clinical opinion to supplement the available ravulizumab trial data. The key assumptions of the primary economic analysis are described in Table 46. Key assumptions relating to the secondary analysis are presented in Appendix N.3.

Table 46: Summary of model assumptions

Topic	Assumption	Justification/reason
Efficacy	Ravulizumab and eculizumab have the same efficacy.	Data from the PNH trial show non-inferiority between treatment arms.[49, 50] Results from the ITC show no systematic, clinically relevant or significant differences between arms.[100] Clinical opinion suggests that they would expect similar outcomes.[24]
Treatment discontinuation	Patients with a misdiagnosis are confirmed within 1 month.	Clinical opinion suggests that diagnoses of patients with aHUS are correctly confirmed within 1 month.[24]

Topic	Assumption	Justification/reason
	Treatment discontinuation represents the 'general' reasons patients discontinue using an exponential distribution.	The clinical trials had no set discontinuation criteria. Consequently, patients mainly discontinued for adverse events or patient preferences, and therefore, data from the trials are more representative of these general reasons. Without any other information to inform selection of the most appropriate distribution, and given that these could happen at any time, the exponential distribution assuming a constant rate over time seems appropriate.
	Patients who discontinue due to no renal response will not discontinue until at least 6 months post ravulizumab treatment.	This is based on the ravulizumab SmPC, which states a minimum treatment duration of 6 months.[1] This contradicts clinical opinion, which does not see the need of an additional 3 months of ravulizumab treatment compared to eculizumab[24], and therefore, this assumption is considered conservative.
Treatment costs	Children's weights increase linearly over time but become constant at the age of 18.	To represent accurate treatment costs for children whose weight increases with age, data from the RCPCH UK-WHO growth charts were used to calculate the average growth rate per 6 months for children under 18.[94, 95] The data show an approximately linear trend, and therefore, a linear increase was deemed appropriate.
	Treatment monitoring costs for children are the same as those for adults.	There is limited data to inform specific paediatric monitoring costs. These costs are applied to both treatment arms, so the impact is likely to be minimal.
	Patients who reinitiate treatment remain on treatment for life.	Many factors might cause patients to discontinue treatment again; however, due to a lack of data and for simplicity, it is not considered in this model.
Key: ITC, indirect treatment comparison; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics; RCPCH, Royal College of Paediatrics and Child Health; WHO, World Health Organization.		

B.3.7. Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

Base case results of the cost-effectiveness comparison between ravulizumab and eculizumab, using the PAS, are presented in Table 47. Adult and child populations are modelled separately with the results weighted based on the proportion of adults ([redacted]) versus children ([redacted]) currently treated in clinical practice (based on personal communication from the NRCTC as of August 2020) to create a single set of results. Results for each population are presented separately in Appendix R. These results assume the same efficacy between ravulizumab and eculizumab and show a total [redacted] decrease in costs for ravulizumab compared to eculizumab (total saving [redacted]).

Disaggregated results are presented in Table 48 and indicate that drug costs are the primary driver of cost savings within the model. Based on these results, ravulizumab is considered cost saving compared to eculizumab.

Table 47: Same efficacy applied – base case results (PAS price)

Costs	Eculizumab	Ravulizumab
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
Key: PAS, patient access scheme.		

Table 48: Same efficacy applied – base case disaggregated results (PAS price)

	Ravulizumab	Eculizumab	Incremental costs (£)		
Parameter	**Costs (£)**	**Costs (£)**	**Increment**	**Absolute inc**	**% abs increment**
Pre-discontinuation health state costs					
CKD Stage 0–2	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
CKD Stage 3a–3b	[redacted]	[redacted]	[redacted]	[redacted]	0.001%
CKD Stage 4	[redacted]	[redacted]	[redacted]	[redacted]	0.001%
CKD Stage 5	[redacted]	[redacted]	[redacted]	[redacted]	0.010%
Transplant	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
Transplant success	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	0.008%
aHUS relapse	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
Post relapse health state costs	[redacted]	[redacted]	[redacted]	[redacted]	
CKD Stage 0–2	[redacted]	[redacted]	[redacted]	[redacted]	0.001%
CKD Stage 3a–3b	[redacted]	[redacted]	[redacted]	[redacted]	0.001%
CKD Stage 4	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
CKD Stage 5	[redacted]	[redacted]	[redacted]	[redacted]	0.002%
Transplant	[redacted]	[redacted]	[redacted]	[redacted]	0.000%
Transplant success	[redacted]	[redacted]	[redacted]	[redacted]	0.000%

	Ravulizumab	Eculizumab	Incremental costs (£)		
Parameter	**Costs (£)**	**Costs (£)**	**Increment**	**Absolute inc**	**% abs increment**
Drug and administration costs	[redacted]	[redacted]	[redacted]	[redacted]	99.975%
Total	[redacted]	[redacted]	[redacted]	[redacted]	**100%**
Key: aHUS, atypical haemolytic uremic syndrome; CKD, chronic kidney disease; PAS, patient access scheme.					

B.3.8. Sensitivity analyses

Probabilistic and deterministic sensitivity analysis was conducted to explore the uncertainty in the model results. The sensitivity analysis for the primary analysis is presented below; the sensitivity analysis for the differential scenario is presented in Appendix N.

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed within the model for 1,000 iterations. The mean incremental costs from ravulizumab versus eculizumab are displayed in Table 49. The visual results of the PSA runs are displayed in Figure 22.

The overall mean probabilistic values are similar to the deterministic values and conclude that ravulizumab is cost saving versus eculizumab in 100% of the 1,000 PSA iterations run.

Table 49: Mean results of PSA (1,000 runs) and comparison with deterministic results

Technology	Total costs (£)		Incremental costs	
	PSA	Deterministic	PSA	Deterministic
Eculizumab	[redacted]	[redacted]		
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: PSA, probabilistic sensitivity analysis.				

Figure 22: Spread of incremental costs (1,000 PSA runs)

Key: PSA, probabilistic sensitivity analysis

B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis was conducted to explore the sensitivity in the deterministic base case model results when one parameter is varied at a time between its lower and upper bounds. Appendix Q summarizes the parameters varied in the one-way sensitivity analysis and the lower and upper bounds used.

The top 10 influential parameters on the incremental costs for the ravulizumab PAS price are presented as a tornado diagram in Figure 23 and in tabular format in Table 50. The parameters with the largest impacts are the relapse rates, length of aHUS diagnosis period and treatment discontinuation. Ravulizumab remained cost saving for all parameters tested.

Figure 23: Incremental costs tornado diagram (PAS price)

Key: CKD, chronic kidney disease; ECU, eculizumab; ESRD, end-stage renal disease; PAS, patient access scheme.

Table 50: OWSA tornado table, lower and upper values (PAS price)

Parameter	Lower bound incremental cost	Upper bound incremental cost	Absolute difference
ECU: relapse rate (adults)	[redacted]	[redacted]	[redacted]
Length of diagnosis period (months) – ECU	[redacted]	[redacted]	[redacted]
Proportion of patients who discontinue for misdiagnosis	[redacted]	[redacted]	[redacted]
ECU: relapse rate (children)	[redacted]	[redacted]	[redacted]
ECU: CKD Stage 3a–3b excess mortality rate (adults)	[redacted]	[redacted]	[redacted]
ECU: ESRD excess mortality rate (adults)	[redacted]	[redacted]	[redacted]
ECU: CKD Stage 0–2 excess mortality rate (adults)	[redacted]	[redacted]	[redacted]
Percentage with prior transplant	[redacted]	[redacted]	[redacted]
Cost of a nurse specialist	[redacted]	[redacted]	[redacted]
ECU proportion who have home care (adults)	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; ECU, eculizumab; ESRD, end-stage renal disease; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

B.3.8.3 Scenario analysis

The worst-case scenario analysis using differential efficacy for CKD stage based solely on the ITC (Table 51) also shows that, compared to eculizumab, ravulizumab reduces costs by [redacted] (a total saving of [redacted]). Using efficacy data from the ITC, the results show a decrease in QALYs ([redacted]) for ravulizumab compared to eculizumab. Therefore, the ICER sits within the South-West quadrant of the cost-effectiveness plane and remains well above the threshold to consider eculizumab more cost-effective than ravulizumab ([redacted]). The negative QALYs are due to more patients in the ravulizumab arm being predicted to transition to the CKD 5 health state (which has higher mortality rates, an increased possibility of transplants and lower utilities). These differences are not considered plausible based on the evidence of no systematic or statistical differences and on expert opinion of expected similarities.

Table 51: Cost-effectiveness analysis using the ITC – scenario analysis results (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	iNMB (WTP £30,000)
Eculizumab	[redacted]	[redacted]	[redacted]					
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; iNMB, incremental net monetary benefit; WTP, willingness to pay.
Notes: Adults represent [redacted] of the combined adult and children population.

Additional scenario analyses were performed to analyse the effect of varying a given model parameter on the base case model results. The results of the scenario analyses are presented below in Table 52 at the ravulizumab PAS price.

The scenarios with the largest impact are those related to discounting and treatment discontinuation. Ravulizumab remained cost saving for all scenarios tested.

Table 52: Scenario results (PAS price)

Scenario category	Base case	Scenario	Incremental costs (£)	Change from base case incremental cost (£)
Base case			[redacted]	
Discount rates	Costs: 3.5%	0%	[redacted]	[redacted]
		6%	[redacted]	[redacted]
Time horizon	100 years	20 years	[redacted]	[redacted]
		50 years	[redacted]	[redacted]
		70 years	[redacted]	[redacted]
Patient weight data	All patients	Using European patients only	[redacted]	[redacted]
Treatment discontinuation	Diagnosis period included	Excluded	[redacted]	[redacted]
	General discontinuation using pooled ITC	Treatment specific	[redacted]	[redacted]
		aHUS registry	[redacted]	[redacted]
	Treatment discontinuation for no renal response included	Excluded	[redacted]	[redacted]
	Ravulizumab discontinuation due to no renal response time is 6 months	Same as eculizumab (3.5 months)	[redacted]	[redacted]
	Discontinuation due to renal recovery excluded	65% discontinue at 6 months due to renal recovery	[redacted]	[redacted]
		25% discontinue at 6 months due to renal recovery	[redacted]	[redacted]
	Exponential	Generalized gamma	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]

Scenario category	Base case	Scenario	Incremental costs (£)	Change from base case incremental cost (£)
Treatment discontinuation curve distributions		Log-logistic	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]
Treatment discontinuation curve distributions (prior transplant only)	Exponential	Generalized gamma	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]
Patients with prior transplant	20.9%	30% as per clinician feedback on expected UK %	[redacted]	[redacted]
Key: aHUS, atypical haemolytic uremic syndrome; CKD, chronic kidney disease; PAS, patient access scheme.				

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analysis results demonstrate the robustness of the base case conclusion that ravulizumab is cost saving versus eculizumab.

The probabilistic results are consistent with the deterministic results, and ravulizumab remained cost saving in 100% of PSA iterations. OWSA identified the parameters with the biggest impact on the incremental costs and qualified the impacts of taking extreme values of each parameter on the model results. The OWSA showed that the model results were not overly sensitive to these parameters, with all incremental cost values remaining in favour of ravulizumab.

A wide range of scenarios were performed to assess the key model assumptions and alternative choices on model results. All scenarios were consistent with the base case conclusion that ravulizumab is cost saving, even the worst-case scenario analysis, which assumes that eculizumab is more effective than ravulizumab.

B.3.9. Subgroup analysis

Results for the adults and paediatric subgroups are supplied in Appendix R and are consistent with the base case.

B.3.10. Validation

B.3.10.1 Validation of economic analysis

The following key aspects of the model methods and inputs were validated by health economic and clinical experts following a virtual advisory board[24]:

- The model structure and its appropriateness to reflect the clinical pathway
- Assumptions in the efficacy inputs to compare ravulizumab to eculizumab
- Extrapolation of treatment discontinuation
- Data sources considered to inform resource use costs
- Clinical validity of utilities derived from the clinical trials

In addition to the above, internal and external data sources were used to validate the projected model survival outcomes and internal sources were used to validate the treatment discontinuation outcomes. Validation of the model survival outcomes are

presented in Appendix N.5 using the results of the scenario analysis investigating differential efficacy informed by the ITC.

B.3.10.2 Internal validation

B.3.10.2.1 Time to treatment discontinuation

Internal validation uses the TTD KM data from the weighted trial data to compare the model treatment discontinuation outputs. Table 53 shows the model-projected TTD compared to the KM from the weighted trial data. To make the comparison fair, only general treatment discontinuation was compared with the raw data, as other treatment discontinuations came from alternative sources and therefore would not compare to the weighted trial data. The modelled TTD shows similar estimates when compared with the weighted pooled trial data.

Table 53: Trial KM TTD versus model TTD

	Data median (years)	Year 1	Year 2	Year 3	Year 4	Year 5
Adults – no prior transplant						
Weighted trial data (KM)	5.5	86.8%	78.3%	64.4%	57.4%	51.0%
Model TTD	5.2	87.6%	76.7%	67.2%	58.9%	51.6%
Adults – prior transplant						
Weighted trial data (KM)	2.7	94.8%	75.2%	45.0%	45.0%	35.3%
Model TTD	4.8	86.6%	74.9%	64.8%	56.1%	48.6%
Children						
Weighted trial data (KM)	NA	93.8%	90.3%	85.5%	75.9%	51.7%
Model TTD	7.4	91.1%	82.9%	75.5%	68.8%	62.6%
Key: KM, Kaplan–Meier; TTD, time to treatment discontinuation.						

B.3.11. Interpretation and conclusions of economic evidence

The economic analysis performed is based on a previous model (HST1) taking in feedback from the ERG and committee, with a structure designed to reflect the aHUS pathway in UK clinical practice and to capture the relevant outcomes. The model structure is consistent with the previous HST1 submission with added health states around treatment discontinuation, capturing an important element of the aHUS pathway for eculizumab and ravulizumab.

The key limitation of the analysis is the lack of comparative data between ravulizumab and eculizumab; however, due to the availability of patient-level data for both trials, robust statistical techniques were used to adjust the patient populations to make a fairer comparison. Additionally, a lack of evidence for patients with aHUS in the literature in general, especially for the paediatric population, meant relying on assumptions and clinical opinion to inform model inputs.

Although there is a lack of head-to-head trial data informing a comparison between eculizumab and ravulizumab, there is an abundance of evidence suggesting that these two treatments have similar efficacy. Head-to-head data from the PNH trials confirm non-inferiority between the two arms, similar outcomes were observed in the aHUS clinical trials and clinical opinion confirms no expectation of any differences. The ITC confirms these expectations, demonstrating no clinically relevant or statistically significant differences between treatment groups and, although some numerical differences were observed, these did not represent consistent trends in favour of one treatment or the other. Considering that the two treatments are effectively the same apart from the moderated half-life, and the evidence described above, there is no reason to suggest clinical differences between ravulizumab and eculizumab.

Based on the strong evidence of non-inferiority, a cost-minimization approach has been presented showing a [redacted] reduction in total costs per person (total saving of [redacted]) for ravulizumab compared to eculizumab, which is mainly due to drug costs from the drastically reduced number of infusions required for patients on ravulizumab.

The model also presents a cost-effectiveness analysis as a scenario analysis using the efficacy for CKD stage solely estimated from the ITC. The survival estimates of the eculizumab arm were validated against external sources showing consistent outcomes (Appendix N.5). This scenario analysis showed lower QALYs ([redacted]) for the ravulizumab patients compared to the eculizumab patients due to more patients in the ravulizumab arm being predicted to transition to the CKD 5 health state (which has higher mortality rates, an increased possibility of transplants and lower utilities). Based on the evidence mentioned previously on the expected similar outcomes, it

seems implausible to believe that more patients on ravulizumab would have renal failure, require a transplant and/or die compared to those on eculizumab. Despite this worst-case scenario analysis showing worse outcomes for ravulizumab, it still demonstrated a [redacted] reduction in costs (total saving [redacted]) compared to eculizumab, concluding that ravulizumab is considerably more cost-effective than eculizumab at the £20–£30,000 willingness to pay threshold. This conclusion is robustly supported by the array of sensitivity analysis undertaken where ravulizumab remained cost-effective for every PSA iteration, parameter variation and scenario tested (Appendix N.4). Moreover, based on a saving of [redacted], ravulizumab would need to demonstrate a QALY loss of at least [redacted] before eculizumab would be considered more cost effective than ravulizumab, which is considered wildly implausible.

Despite the limitations of the analysis for the clinical comparison, ravulizumab offers drastic savings to the NHS and benefits patients through less frequent dosing with no evidence to suggest worse outcomes.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional data from ravulizumab trials

Appendix M: Health-related quality of life analysis

Appendix N: Worst case scenario analysis: differential efficacy using ITC

Appendix O: Additional model scenarios

Appendix P: Ordinal probit models

Appendix Q: Base case parameters and distributions

Appendix R: Additional model results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID1530 Ravulizumab ALEXION response to ERG Clarification letter	V1	Yes	11 November 2020

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Positioning of ravulizumab

A1. Priority question: In the absence of direct trial evidence for adults with aHUS who have received eculizumab for at least 3 months and have evidence of response to eculizumab, please provide available evidence to support a recommendation for ravulizumab use in this population.

Uncontrolled terminal complement activation is central to the pathogenesis of aHUS. The targeted blockade of C5 with complement inhibitor represents an important therapeutic mechanism and is the only pharmacological treatment with established efficacy in aHUS. Ravulizumab and eculizumab share this fundamental mechanism of action, that is, targeting complement component C5 with high affinity.

Clinical evidence to support a recommendation of ravulizumab use in adults with aHUS who have received eculizumab for at least 3 months and have evidence of response to eculizumab include:

1. Data from Cohort 2 of the ALXN1210-aHUS-312 trial (n=10) – these are fully detailed in the company submission (CS) and show that paediatric and adolescent patients (<18 years of age) with aHUS who were clinically stable following ≥90 days treatment with eculizumab maintained disease control following a ‘switch’ to ravulizumab. Complete free C5 inhibition data (Figure

10 of the CS) further show maintained target complement C5 inhibition throughout the dosing interval when patients are 'switched' from eculizumab.

2. Data from the Phase III ALXN1210-PNH-302 trial (n=197) – these are summarized in the CS but are further detailed in Table 1. Data show that adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who were clinically stable following ≥6 months treatment with eculizumab maintained target complement C5 inhibition and disease control following a 'switch' to ravulizumab. Data also show ravulizumab was statistically non-inferior to eculizumab across all efficacy endpoints in this patient group.

Table 1: ALXN1210-PNH-302 trial evidence

Trial methodology			
Study design	Phase III Open-label; parallel assignment Non-inferiority Randomized Period: 26 weeks Extension Period: up to 2 years		
Population	Adult patients with PNH who are clinically stable following ≥ 6 months treatment with eculizumab		
Intervention (n)	Ravulizmab (n=97)		
Comparator (n)	Eculizumab (n=98) In the Extension Period, all patients were treated with ravulizumab		
Objective	To assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are clinically stable following ≥ 6 months treatment with eculizumab.		
Trial outcomes			
	Ravulizumab (n=97)	**Eculizumab (n=98)**	**Treatment effect[a] (95% CI)**
Percent change in LDH, LSM (95% CI)[b]	-0.82 (-7.8, 6.1)	8.4 (1.5, 15.3)	9.21 (-0.42, 18.8)
BTH rate, % (95% CI)	0 (0, 3.7)	5.1 (1.7, 11.5)	5.1 (-8.9, 19.0)
Change in FACIT-Fatigue score, LSM (95% CI)	2.0 (0.6, 3.4)	0.54 (-0.8, 1.9)	1.5 (-0.2, 3.2)
Transfusion avoidance rate, % (95% CI)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)	5.5 (-4.3, 15.7)
Haemoglobin stabilization rate, % (95% CI)	76.3 (67.8, 84.8)	75.5 (67.0, 84.0)	1.4 (-10.4, 13.3)
Key: BTH, breakthrough haemolysis; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; LSM, least squares mean; PNH, paroxysmal nocturnal haemoglobinuria.			

Notes: [a], treatment effect is estimated as difference: ravulizumab–eculizumab except for percent change in LDH and breakthrough haemolysis rate, where treatment effect is estimated as difference: eculizumab–ravulizumab; [b], primary endpoint of trial.
Source: Kulasekararaj et al. 2019.[1]

The aHUS clinical development programme was initiated concurrently with the PNH clinical development programme. During consultation with regulatory agencies, a common ravulizumab dosing strategy for the treatment of aHUS and PNH and the reliance on a single pivotal study to support approval in each indication was agreed. Based on the data described above, the European Medicines Agency (EMA) considered a marketing authorization for the treatment of patients with aHUS, regardless of the previous treatment with eculizumab, acceptable provided that patients have been treated with eculizumab and are stable.[2]

Following market launch of ravulizumab in the US, the aHUS alliance Global Action sent out a call to the aHUS community appealing for volunteers who had experienced treatment with eculizumab and switched to ravulizumab to participate in a Global Action research study on the comparative impact on patients of the two technologies.[3] Although the call for volunteers was to global aHUS patients, only patients from the US offered to participate. While these patients may not fully reflect the UK patient, their insight does provide further evidence supporting a 'switch' from eculizumab to ravulizumab. Ten adult patients and three carers of paediatric patients responded to the appeal and participated in online interviews; patients had 'switched' to ravulizumab (from eculizumab) 4 to 10 months before study participation. Responses to study questions indicate that respondents were generally confident that ravulizumab was as effective at treating their aHUS as eculizumab had been. Several respondents noted that their blood results showed little difference following their 'switch' to ravulizumab, with one respondent reporting a slight improvement on ravulizumab compared with eculizumab. Respondents' experiences of side effects were mixed, with some reporting similar side effects with both treatments, some reporting reduced side effects with ravulizumab over eculizumab and some reporting increased side effects. One patient reported a serious side effect with ravulizumab that warranted a 'switch' back to eculizumab but full details of the reasoning were not provided. In the ALXN1210-PNH-302 trial, there were no discontinuations due to adverse events in patients 'switching' from eculizumab to ravulizumab[1], and the EMA concluded that the safety of ravulizumab and eculizumab appear similar, as detailed

in our response to question A3 below. All respondents in the Global Action research study referred to the longer infusion intervals as a key benefit of ravulizumab treatment (compared with eculizumab), using descriptions including “game changer”, “improved freedom” and “convenience” to convey the impact on their experience of treatment.

A2. Priority question: Does the company expect that all adults with aHUS who have not had complement-inhibitor treatment (‘complement-therapy naïve patients’), and who are considered eligible for complement-therapy, would receive ravulizumab as first-line treatment, or is it expected that some patients would receive ravulizumab as second-line/maintenance treatment following evidence of disease response to eculizumab? Please detail which eligible patients, if any, may be preferred for treatment with eculizumab as first-line.

As per the marketing authorization, ravulizumab could be considered as a treatment option for patients with a body weight of 10 kg or above who are complement inhibitor treatment-naïve (first-line treatment) or have received eculizumab for at least 3 months and have evidence of response to eculizumab (second-line/maintenance treatment).

As acknowledged throughout the CS, the diagnosis and management pathway for aHUS in the UK is complex and evolving. Complement inhibitor treatment is often initiated in parallel to ongoing screening for potential causes of thrombotic microangiopathy (TMA) and response to complement inhibitor treatment is part of the diagnostic pathway. Discontinuation of complement inhibitor treatment is also considered for both lack of renal recovery and stabilization/normalization of renal function.

Where there is uncertainty around the need for long-term (≥6 months) complement inhibitor treatment, it may be that clinicians would choose to use eculizumab over ravulizumab. At a UK advisory board, clinical experts acknowledged that the following patient groups may benefit the most from ravulizumab treatment[4]:

1. Patients with a known complement regulatory gene/protein mutation
2. Patients with a family history of aHUS or relapse history

3. Patients who are dissatisfied with eculizumab due to administration and/or travel-related burden

These patient groups are represented across the first-line and second-line/maintenance settings and we expect clinicians and patients to want the option of treatment with eculizumab or ravulizumab based on their individual circumstances.

Generalisability of the trial populations

A3. Priority question: Please explain to what extent the ravulizumab trial evidence on safety and efficacy in 'complement-therapy naïve patients' is generalisable to adult patients with aHUS whose disease has evidence of response to eculizumab.

The ravulizumab trial evidence on safety and efficacy in 'complement-therapy naïve patients' represents a different patient group at baseline to patients with aHUS whose disease has evidence of response to eculizumab, however, the safety and efficacy profile of ravulizumab is consistent across patient groups.

For patients with complement inhibitor treatment-naïve disease, the aim of treatment is to normalize haematological parameters and improve renal function. For patients whose disease has evidence of response to eculizumab, the aim of ravulizumab treatment is to maintain haematological stabilization and renal function. The majority of complement inhibitor treatment-naïve patients enrolled to ALXN1210-aHUS-311 and Cohort 1 of ALXN1210-aHUS-312 had achieved normalization of haematological parameters and improvement in renal function at the end of the Initial Evaluation Period (26 weeks), that is, their disease had evidence of response to ravulizumab. Ravulizumab shares over 99% homology with eculizumab and the same fundamental mechanism of action (see response to A1). We could therefore consider patients with evidence of response to ravulizumab at the end of the Initial Evaluation Period a good proxy for patients with evidence of response to eculizumab. Continued ravulizumab treatment throughout the Extension Period of ALXN1210-aHUS-311 and ALXN1210-aHUS 312 maintained haematological stabilization and renal function.

As detailed in our response to A1, the EMA considered it acceptable to issue a marketing authorization for the treatment of patients with aHUS, regardless of the

previous treatment with eculizumab, provided that patients have been treated with eculizumab and are stable.[2] More specifically to safety, the EMA noted that the safety profile of ravulizumab in aHUS appears to be comparable to that observed in adult patients with PNH (the PNH trial programme did not include paediatric patients as PNH is extremely rare in children), and that the safety profile in paediatric patients appears similar to that of adults.[2] The EMA had previously concluded that the safety profile of ravulizumab appears similar to that of eculizumab in patients with PNH, both in complement-inhibitor naïve patients and in patients clinically stable on eculizumab treatment.[5]

A4. Priority question: In Document B page 99, it states "Those that would be less likely to be treated with complement-inhibitor treatment in UK practice generally had the worse outcomes, including those patients who died in ALXN1210-aHUS-311." Please clarify which patient subgroups (other than the patients who died) would be considered less likely to receive treatment in England, and the reasons why.

This statement is based on patients who died and patients who had a worsening in CKD stage. All of these patients presented with significant extrarenal signs and symptoms and/or relevant medical history/comorbidities. According to UK clinicians who were asked in an advisory board to consider the trial data, these patients would likely be classed as high-risk 'late presenters' in UK practice with little expectation of a response to complement-inhibitor treatment. Specifically on those patients who died, UK clinicians stated they would "probably not have been treated with ravulizumab in UK clinical practice" when asked to comment.[6]

Additional data for trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312

A5. Priority question: Please provide appendices (complete section 16) for the Clinical Study Reports of trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312

Appendices requested are provided alongside this response document.

Trial ALXN1210-aHUS-311

A6. Priority question: The company refer to two main sources of interpretation for the four participant deaths in ALXN1210-aHUS-311, including whether any could be

related to ravulizumab. The main trial publication (ref 34. in Document B, page 161) stated that none of the deaths were deemed related to the study drug, whilst the recent UK advisory board (ref. 24 in Document B, page 160) stated that it was "difficult to draw any definitive conclusion from the data presented and not possible to say with certainty that these deaths were not treatment-related." Please clarify what the conclusions are for the interpretation of the 4 participant deaths?

The conclusions for the deaths that occurred in the study, as stated in the Clinical Study Report[7] and the Rondeau trial publication[8], are that these were assessed by the Investigator to be unrelated to study drug. As it is important for Alexion to understand UK-specific clinician views on the trial data, the summary narratives of the patient deaths were shared at the recent UK advisory board, and the clinician feedback on this is summarised in the submission document. The UK clinician feedback was based only on the brief narratives provided and does not represent the conclusion of the 311 Study Investigator or the Alexion position.

A7. Priority question: Trial ALXN1210-aHUS-311 Clinical Study Report, Figure 2, shows that the total number of patients excluded due to physician decision was 8 across the initial evaluation period and extension period. Please provide the reasons for the physician decision

As detailed in Figure 2 and the accompanying footnote, only 5 patients discontinued drug treatment due to physician decision, rather than the 8 patients cited in question A7. This included 1 patient in the Initial Evaluation Period (0044-603) and 4 patients in the Extension Period (0044-605; 0297-606; 0596-601; 0733-601). Please note, the three patients who are shown in Figure 2 to have discontinued study drug while remaining in the study without treatment are already counted in the Extension Period discontinuations and are therefore not additional discontinuations; two of these three patients (0297-606 and 0733-601) discontinued due to physician decision.

The reasons for the physician decision to discontinue from treatment for each of the 5 patients is listed in the table below.

Table 2: Reasons for physician decision to discontinue treatment in ALXN1210-1210-311

Patient ID	Initial Evaluation Period (IEP)	Extension Period (EP)	Reason	Comments
0044-603	Discontinued from Treatment Discontinued from IEP	-	Physician decision	PI withdrew the patient for an alternative diagnosis, sepsis from fungemia. The patient was treated with antifungals and TMA resolved
0044-605	Completed IEP	Discontinued from Treatment Discontinued from EP	Physician decision	cTMA responder; physician judgement of low risk for disease recurrence or relapse
0297-606	Completed IEP	Discontinued from Treatment	Physician decision	cTMA responder; PI decision no further treatment required after initial evaluation period
0596-601	Completed IEP	Discontinued from Treatment Discontinued from EP	Physician decision	Postpartum; cTMA responder; patient and PI agreed on study discontinuation
0733-601	Completed IEP	Discontinued from Treatment	Physician decision	Remained with ESRD on dialysis; PI and patient decided on no further treatment

Key: cTMA, complete thrombotic microangiopathy; EP, Extension Period; ESRD, end stage renal disease; IEP, Initial Evaluation Period; PI, principal investigator; TMA, thrombotic microangiopathy.
Source: Alexion data on file.

A8. Priority question: Subgroup analyses in trial ALXN1210-aHUS-311 showed better complement-gene-variant-mediated thrombotic microangiopathy (cTMA) outcomes in the European site subpopulation, compared with the Asian and North America sites.

Please note cTMA is the abbreviation used for complete thrombotic microangiopathy, as described in the CS and not complement-gene-variant-mediated thrombotic microangiopathy as defined in this question.

a. Please provide an explanation for this result, in addition to reasons provided in Section B.2.13.2.2, pages 98 and 99?

Given the small numbers involved and the lack of statistical power in relation to the data set by subgroup, it is difficult to draw any meaningful conclusions on the

comparisons across the geographic subgroups analysed. The North American numbers in particular (n=6) are very small with a very wide confidence interval so that comparisons particularly in this group should not be made. It is possible that patients recruited to the Asian sites may have presented later in their disease pathway compared to those at the European sites, and as such intervention was not sufficiently timely to result in a full response. As already cited in the CS, it is thought any difference is more due to these differences in diagnosis and management pathways rather than an underlying difference due to ethnicity.

b. Please comment on why this difference in cTMA outcomes was not observed in the paediatric trial data.

The numbers available in the subgroup analysis for the paediatric population in the ALXN1210-aHUS-312 study are even smaller compared to the ALXN1210-aHUS-311 study, and no geographical variance was observed. This is consistent with previous statement that any differences which might exist are unlikely to be a reflection of ethnic variance. In addition, the paediatric population of aHUS tends to be more homogenous by nature of the disease and approach to management, which may also account for a more consistent picture across the subgroup analysis.

A9. In Table 24 Document B, pages 90 and 91 (Summary of safety results for the aHUS ravulizumab trials) and Table 35, pages 131 and 132 of ALXN1210-aHUS-311 Clinical Study Report, aHUS is listed as a serious adverse event. Please explain why

AEs and SAEs can occur any time after consent which includes screening. The two patients (3.4%) with aHUS listed as an SAE were two cases of patients with the TMA inclusion criteria in whom aHUS was confirmed during screening. The principal investigators (PI) opted to report the diagnosis as an AE in these two instances.

Indirect treatment comparison

A10. Priority question: Given the clinical relevance of complement regulatory gene/protein mutations or anti-CHF autoantibodies and differences in prevalence in the ravulizumab trial population compared with the eculizumab trial and real-world

populations (as noted in Document B, page 98), please clarify why matching for these characteristics was not performed.

It is important to note that while a number of genetic variants and the presence of autoantibodies to complement proteins have been identified as the underlying driver of disease in a significant proportion of aHUS patients, not all patients have identified genetic markers. Indeed, as detailed in the CS, published analyses suggest only 45-70% of diagnosed aHUS patients have either a currently identifiable underlying genetic mutation or anti-complement autoantibodies.[9-12] In the UK, based on the most recent NRCTC report, 69% of aHUS patients who are currently treated with eculizumab, have an identified genetic variant.[13]

The characteristics considered important for matching in the indirect treatment comparison (ITC) were selected by expert clinicians with experience of managing patients with aHUS and then ranked in order of importance. If any variables needed to be excluded due to sample size, then the ranking allowed the most important variables to be matched first. Complement regulatory gene/protein mutations and anti-CHF- autoantibodies were not discussed as part of the clinical validation process or raised by clinicians as an important variable for balancing populations in the ITC.

If matching by genetic variant or auto-antibodies had been cited as important, in order to have considered matching patients in the ITC by these characteristics, the relevant data would need to be available for patients across both the eculizumab and ravulizumab cohorts included in the analysis. As assessments of genetic variants and presence of autoantibodies to complement proteins were assessed only as exploratory analyses in the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 studies, they were performed in a limited number of consenting patients only (Table 3). Moreover, as genetic analysis in this area has moved on since the eculizumab trials were conducted, and new variants have been identified in recent years, any comparison between eculizumab and ravulizumab would not be possible on a like for like basis. With data on genetic variants only available in a limited number of ravulizumab patients, and no like-for-like comparison possible, it is not feasible to match patients on the basis of their genetic variants in the ITC.

Table 3: Number of patients with pathogenic variants or autoantibodies

Study	Number of patients tested for both pathogenic variant or autoantibody	Proportion of total patients with ≥1 identified variant or autoantibody
ALXN1210-aHUS-311	39/56 (70%)	8/56 (14%)
ALXN1210-aHUS-312 Cohort 1	10/18 (56%)	9/18 (50%)
ALXN1210-aHUS-312 Cohort 2	4/10 (40%)	3/10 (33%)

A11. Priority question: Please provide justification for why patients with greater than one missing laboratory variables were excluded from the analysis. In addition, please provide the numbers for how many patients were excluded for this reason for ravulizumab and eculizumab in each of the populations analysed (adults non-transplant, adults with transplant, children non-transplant).

In order for the ITC outcomes to be compared, three of the four key laboratory measures (estimated glomerular filtration rate [eGFR], lactate dehydrogenase [LDH], creatinine for non-dialysis patients and platelet count) at either baseline or endpoint were required, hence patients with greater than one missing variable were removed from the analysis. No imputation of missing data was performed given the trials were registration studies with high rates of completion, and hence this only affected a minimal number of patients. The total number of patients excluded for having one missing variable is summarised in Table 4.

Table 4: Number of patients with greater than one missing key laboratory measure

Population	Eculizumab	Ravulizumab	Total
Adults (non-transplant)	[redacted]	[redacted]	[redacted]
Adults with transplant	[redacted]	[redacted]	[redacted]
Children (non-transplant)	[redacted]	[redacted]	[redacted]

A12. Document B, Table 26, page 106, states “only CKD stage information is taken forward into the model, whereas for other endpoints the ITC shows mostly benefit for ravulizumab vs eculizumab.” This statement does not seem to be consistent with the

interpretation of the indirect treatment comparison (ITC) results in B.2.9.2.2 page 76 and B.2.13.1.pages 96 and 97. Please clarify this inconsistency.

Apologies for the oversight. This interpretation was based on early analyses and not updated in line with the final analyses that showed no consistent trends in favour of one treatment or the other (as discussed in B.2.9.22 and B.2.13.1).

A13. Priority question: In Document B, page 98 it states, "An ITC demonstrated no statistically significant or clinically relevant differences in effectiveness when formally comparing ravulizumab with eculizumab". Please explain how "clinically relevant differences" were defined? In addition, please clarify whether these criteria were determined before analyses were conducted.

Criteria for determining clinically relevant differences between treatments were not pre-defined but rather were determined through clinical consultation. Experts were asked to comment on whether there were any clinically relevant differences observed in a selection of data sets prior to ITC outcomes being revealed. Criteria for determining clinically relevant improvements from baseline were determined before analyses were conducted for health-related quality of life (HRQL) outcomes based on minimally important differences for EQ-5D and Functional Assessment of Chronic Illness Therapy (FACIT) scores reported in the literature as:

- 10 points for adult patients on the EQ-5D visual analogue scale[14]
- 3 points for adult patients on the FACIT-Fatigue subscale[15]
- 4.7 points for paediatric patients on the FACIT-Fatigue subscale[16]

Criteria for determining clinically relevant improvements from baseline for some clinical endpoints were also pre-defined as ≥ 25% improvement for serum creatinine and ≥ 20 g/L improvement for haemoglobin.[7, 17] Normal ranges for other clinical endpoints are also well-established as:

- 130–400 10^9/L for platelets
- 120–246 U/L for lactate dehydrogenase
- 130–175 g/L for haemoglobin
- ≥ 60 mL/min/1.73 m^2 for estimated glomerular filtration rate

A14. NICE DSU Technical Support document 18 recommends submissions, “present an estimate of the likely range of residual systematic error in the “adjusted” unanchored comparison.” If not already provided in the submission, please provide either, i) a likely range of residual systematic error, or ii) justify why this is not possible.

Revised question following TC:

a) Please could you justify further why you opted to use methods outlined in TSD17 rather than the methods recommended in TSD18 which provide specific guidance on ITC analyses of single arm trials?

NICE TSD 18 details how comparisons should be performed in two instances, firstly reweighting individual level data to match aggregate level data i.e. when patient level data is not available (unanchored MAIC, and STC), and reweighting data to account for imbalances between trials before inclusion in Network Meta-Analysis (termed anchored MAIC). NICE TSD 17 provides recommendations for the analysis of comparative individual patient data from non-RCTs to obtain estimates of treatment effect.

Given that no common comparator was available for anchoring and individual patient data is available for all treatment arms for this analysis, techniques from NICE TSD 17, were utilised. Using Figures 1-3 in TSD 17 lead to the choice between ‘Inverse probability weighting’, ‘Doubly robust’ and ‘matching’; all of which involve propensity scoring. For this analysis, propensity scoring according to best practice was implemented, for instance using Brookhart et al. 2006 and Austin et al. 2011, preferring matching over weighting to ensure comparability of patients, and performing analyses in subgroups to avoid confounding by indication. [18, 19]

b) Although we agree there are advantages in having access to IPD for all trials, we do not think this is relevant to the issue we are raising. It is generally accepted that residual systematic error (due to unknown prognostic factors or imbalances in effect modifiers) is likely to remain whether you have access to IPD for some or all included trials. Therefore, where possible, please could you present some estimate of the likely range of residual systematic error or a justification of why this is not possible or necessary.

The assessment of residual systematic error is not appropriate for propensity score analysis. This term applies to regression methods. NICE TSD 18 contains suggestions from the authors on measures of residual systematic error (bias resulting from unobserved prognostic variables and effect modifiers) but also notes that further research is necessary to refine and validate these methods (page 66). The context of NICE TSD 18 and our analysis are very different. TSD 18 addresses unanchored comparison across one trial with and one trial without patient level data. We compare two ravulizumab trials with patient level data with three eculizumab trials with patient level data.

Given this, as described above, NICE TSD 17 was used to choose the appropriate method of analysis and hence why propensity score was selected. However, the main limitation of propensity scoring is that groups are balanced on observable characteristics. The residual error is therefore zero based on what we observed; any unobserved characteristics however may not be matched.

Although best efforts (including clinical input and the literature) have been used to inform the matching, it is possible an important variable is omitted as its importance has not been recognised.

The two methods suggested in NICE TSD 18 for characterisation of residual error from unobserved prognostic variables and effect modifiers are:

- Out of sample methods (comparison of prediction to a different dataset)
- In sample methods (cross-validation or R^2 are suggested)

Out of sample comparison was considered. However, given that other datasets not used for the matching are not in the same format and that an out of sample comparison wouldn't necessarily prove or disprove an unobserved covariate this was not considered to be possible or useful.

Considering the in sample methods, the TSD only provides specific guidance on methods for regression analysis or simulated treatment comparison; neither of which are relevant to the comparison we have made. Instead we provide sensitivity and scenario analyses varying the methods used, the characteristics matched on, patient subgroups and the definitions of outcomes. Full cross validation was not possible

due to the small sample sizes (n=12, 7 and 46 for ravulizumab and n=20, 15 and 39 for eculizumab for the paediatric, adults with kidney transplant and adults without kidney transplant respectively). The scenario analysis conducted around the different characteristics being matched on can be seen as having a similar underlying principle to the cross-validation discussed in TSD 18. Scenario and sensitivity analyses were conducted to ensure that the findings were accurate and not specific to the methods or applications chosen and generalisable. Results were consistent in all these methods, and in subgroups, there was nothing in the sensitivity analyses which questioned the robustness of the conclusions (see separate ITC report[20]). However, as expected in a rare disease, the small patient numbers can limit the strength of conclusions that can be drawn.

A further limitation relates to the underlying data which is used for matching. Unavoidably the studies used were conducted approximately 10 years apart, and it is possible that standards of care or diagnosis have evolved in the disease area. This could change the patients enrolled in the trials such that even for the same values of eGFR and platelet count, for example, different outcomes would be expected. This is a structural uncertainty which cannot be explicitly tested for and is considered to be the main limitation of the analysis.

Safety profiles of ravulizumab and eculizumab

A15. Priority question: Document B, page 97 states that “a qualitative synthesis of pivotal trial data suggests no differences in safety profiles”. Please provide further details on the qualitative synthesis methods and results. In addition, please provide a breakdown of the adverse events (including types and severity) in the eculizumab evidence in adults and children (as per Document B, Table 24, pages 90 and 91) and provide a comparison with the ravulizumab evidence to justify this conclusion, including any limitations.

The qualitative synthesis consisted of a naïve comparison of safety data across trials deemed feasible for ITC of clinical and HRQL outcomes. This qualitative synthesis is provided in Appendix F of the company submission (Table 25).

The Global aHUS Registry was not deemed feasible for ITC of clinical and HRQL outcomes due to several data gaps. Safety data are similarly lacking but those

reported in a 5-year experience publication have been including in the expanded qualitative synthesis provided in Table 5.

As detailed in our response to A3, the EMA noted that the safety profile of ravulizumab in aHUS appears to be comparable to that observed in adult patients with PNH (the PNH trial programme did not include paediatric patients as PNH is extremely rare in children), and that the safety profile in paediatric patients appears similar to that of adults.[2] The EMA had previously concluded that the safety profile of ravulizumab appears similar to that of eculizumab in patients with PNH, both in complement-inhibitor naïve patients and in patients clinically stable on eculizumab treatment.[5]

Table 5: Summary of safety results across treatment-naïve populations of ravulizumab and eculizumab trials

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	aHUS-C08-002 NCT00844545	aHUS-C10-003 NCT01193348	aHUS-C10-004 NCT01194973	Global aHUS Registry	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Eculizumab (n=17)	Eculizumab (n=22)	Eculizumab (n=41)	Eculizumab Adult patients (n=535)	Eculizumab Paediatric patients (n=330)
Any adverse event, n (%)	58 (100)	[redacted]	[redacted]	20 (91)	41 (100)	Not reported	Not reported
AE severity n (%)						Not reported	Not reported
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Grade 4	14 (24.1)	[redacted]	[redacted]	[redacted]	[redacted]		
Grade 5	3 (5.2)	[redacted]	[redacted]	[redacted]	[redacted]		
Any TRAE, n (%)	20 (34.5)	[redacted]	12 (71)	9 (41)	[redacted]	Not reported	Not reported
Any SAE, n (%)	33 (56.9)	[redacted]	[redacted]	13 (59)	18 (44)	Not reported	Not reported
Meningococcal infections, n (%)	0 (0)	[redacted]	0	0	2 (4.9)	2 (0.4)	1 (0.3)
DC due to AE, n (%)	3 (5.2)	[redacted]	1 (6)	1 (4.5)	1 (2.4)	Not reported	Not reported
Death, n (%)	4 (6.9)	[redacted]	0	0	0	25 (4.7)	6 (1.8)
Death due to AE, n (%)	3 (5.2)	[redacted]	0	0	0	8 (1.5)[c]	2 (0.6)[c]
Common AEs[a], n (%)						Not reported	Not reported
Headache	[redacted]	[redacted]	[redacted]	–	15 (37)		
Diarrhoea	[redacted]	[redacted]	[redacted]	7 (32)	13 (32)		
Vomiting	[redacted]	[redacted]	[redacted]	6 (27)	–		
Hypertension	[redacted]	[redacted]	[redacted]	–	–		
Nausea	[redacted]	[redacted]	[redacted]	–	–		

	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	aHUS-C08-002 NCT00844545	aHUS-C10-003 NCT01193348	aHUS-C10-004 NCT01194973	Global aHUS Registry	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Eculizumab (n=17)	Eculizumab (n=22)	Eculizumab (n=41)	Eculizumab Adult patients (n=535)	Eculizumab Paediatric patients (n=330)
Arthralgia	[redacted]	[redacted]		–	–		
Pyrexia	[redacted]	[redacted]		–	–		
Cough	[redacted]	[redacted]		8 (36)	8 (20)		
Peripheral oedema	[redacted]	[redacted]		–	9 (22)		
Fatigue	[redacted]	[redacted]		–	–		
Nasopharyngitis	[redacted]	[redacted]		6 (27)	–		
Abdominal pain	[redacted]	[redacted]		7 (32)	–		
Fever	[redacted]	[redacted]		11 (50)	–		
Anaemia	[redacted]	[redacted]	[redacted]	–	–		
URTI	[redacted]	[redacted]	[redacted]	7 (32)	–		
Urinary tract infection	[redacted]	[redacted]	[redacted]	–	–		
Leukopenia	[redacted]	[redacted]	[redacted]	–	–		
Renal impairment	[redacted]	[redacted]	[redacted]	–	–		
Common SAEs[b], n (%)							
Hypertension	3 (5.2)	[redacted]	2 (12)	2 (9)	-	Not reported	Not reported
Pneumonia	3 (5.2)	[redacted]	-	-	-	Not reported	Not reported
Malignant hypertension	2 (3.4)	[redacted]	-	-	-	Not reported	Not reported
Urinary tract infection	2 (3.4)	[redacted]	-	-	-	Not reported	Not reported
Septic shock / sepsis	2 (3.4)	[redacted]	-	-	2 (5)	14 (2.6)	-
aHUS	2 (3.4)	[redacted]	-	-	-	Not reported	Not reported
Viral gastroenteritis	-	[redacted]	-	2 (9)	-	Not reported	Not reported
Abdominal pain	-	[redacted]	-	-	-	Not reported	Not reported

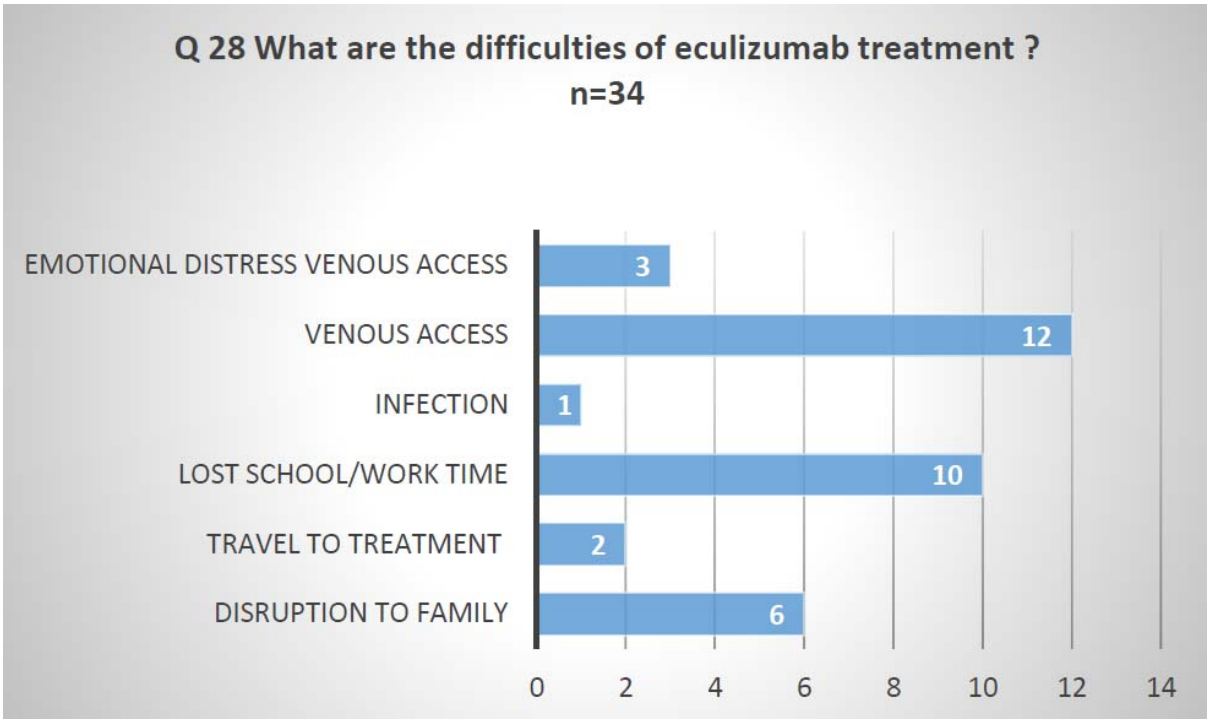
	ALXN1210-aHUS-311 NCT02949128	ALXN1210-aHUS-312 NCT03131219	aHUS-C08-002 NCT00844545	aHUS-C10-003 NCT01193348	aHUS-C10-004 NCT01194973	Global aHUS Registry	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Eculizumab (n=17)	Eculizumab (n=22)	Eculizumab (n=41)	Eculizumab Adult patients (n=535)	Eculizumab Paediatric patients (n=330)
Fever	-	[redacted]	-	2 (9)	-	Not reported	Not reported
URTI	-	[redacted]	-	2 (9)	-	Not reported	Not reported
Serious infection	-	[redacted]	-	-	-	46 (8.6)	32 (9.7)
Convulsion	-	[redacted]	-	-	2 (5)	-	-
Acute renal failure	-	[redacted]	-	-	2 (5)	-	-
Chronic renal failure	-	[redacted]	-	-	2 (5)	-	-
Dyspnoea	-	[redacted]	-	-	2 (5)	-	-
Pulmonary oedema	-	[redacted]	-	-	2 (5)	-	-

Key: AE, adverse event; aHUS, atypical haemolytic uremic syndrome.
Notes: [a], Defined as ≥ 20% of patients – dashes represent events not meeting these criteria in individual trials/cohorts; [b], Defined as >1 patient – dashes represent events not meeting these criteria in individual trials/cohorts; c, death due to infection.
Sources: aHUS-C08-002 CSR[21]; aHUS-C10-004 CSR[22]; ALXN1210-aHUS-311 CSR[7]; ALXN1210-aHUS-312 CSR.[17]; Fakhouri et al. 2016[23]; Greenbaum et al. 2016[24]; Legendre et al. 2013[25]; Rondeau et al. 2019.[26]; Rondeau et al. 2020.[8]

A16. Document B, page 96 states that ravulizumab “could reduce the risk of vein damage" compared with eculizumab. Please clarify whether there is any evidence available to support this.

There are no specific data demonstrating a lower risk of vein damage with ravulizumab compared to eculizumab. However, the complications of long-term intravenous (IV) therapy are well documented, and include among others, venous depletion over time, with a number of these risks associated with repeated IV infusion.[27, 28] Given the frequency and often chronic administration of eculizumab, it is not surprising that both venous access (12/34) and emotional distress related to venous access (3/34) have been identified by aHUS patients as difficulties associated with eculizumab treatment (Figure 1). As ravulizumab represents a treatment option with a very significant reduction in number of annual infusions compared to eculizumab (6–7 vs 26 infusions), it is reasonable to expect a corresponding reduction in the risks associated with chronic, frequent IV infusions.

Figure 1: Difficulties of eculizumab treatment reported by European patients in the Global aHUS Survey



Source: Global aHUS Survey 2016 – European aHUS Patients Voice.[29]

Section B: Clarification on cost-effectiveness data

Cost-effectiveness analysis and economic model

B1. Priority question. The appropriateness of a cost-minimisation analysis (CMA) for evaluating the cost-effectiveness of ravulizumab is dependent not only on the clinical evidence from the trials, but also on evidence relating to health-related quality of life and adverse events. The treatments cannot be considered exactly equivalent given the uncertainty in estimating their effectiveness and safety.

a. Please comment on why uncertainty has not been considered in justifying the use of CMA.

The uncertainty of the effectiveness has been fully explored by providing a cost-effectiveness analysis within the submission as a scenario and providing full deterministic and probabilistic sensitivity analysis results (see Document B, Section B.3.8.3, page 152 and Appendix N). This was considered a worse-case scenario given that the model only considers CKD stage from the ITC with other clinical outcomes not explicitly modelled. CKD stage was one of the clinical outcomes which numerically favoured eculizumab. The CMA was presented as the base case given the evidence supporting equivalent efficacy and lack of evidence supporting the alternative (see Document B, Section B.2.13, Page 96). In addition, the NICE CMA documentation (for the fast-track appraisal), does not require exact equivalence to support the use of the cost-minimisation analysis. Therefore, by providing the CMA and cost-effectiveness analysis as a scenario, we feel we have provided a fully comprehensive analysis assessing the uncertainty on the assumption of equivalent efficacy.

b. The assumption of no clinical difference in efficacy and safety between eculizumab and ravulizumab is based on the lack of statistically significant differences between the 2 treatments from the ITC analysis; however, this analysis is only based on a very small number of patients and only supports the statement that there is not enough evidence to demonstrate any potential differences. Please justify how the assumption of no clinical difference in efficacy and safety is supported by the existing data from eculizumab and ravulizumab studies.

The assumption of no clinical difference in efficacy and safety between eculizumab and ravulizumab is not solely based on the lack of statistically significant differences between the two treatments from the ITC analysis.

Direct evidence is available from Cohort 2 Patients in the ALXN-1210-aHUS-312 trial, who were previously stable on eculizumab and 'switched' to ravulizumab.[30] These patients maintained stability in haematological and renal parameters following treatment switch, demonstrating sustained efficacy of ravulizumab with no unexpected safety concerns.

Ravulizumab was derived from eculizumab and the treatments share over 99% homology and the same fundamental mechanism of action (see response to A1). Differences in their design do not impact the clinical effectiveness or safety of ravulizumab compared to eculizumab, but rather allow a natural recycling of complement-inhibitor that extends its half-life and reduces the frequency of regular infusions (see B.2.12 of the CS for further detail).

Non-inferiority between the two treatments was formally assessed in the PNH trial programme where ravulizumab was shown to be statistically non-inferior to eculizumab.[1, 31] As detailed in our response to A1, the aHUS clinical development programme was initiated concurrently with the PNH clinical development programme. During consultation with regulatory agencies, a common ravulizumab dosing strategy for the treatment of aHUS and PNH and the reliance on a single pivotal study to support approval in each indication was agreed. The EMA also concluded within their variation report for extending the ravulizumab indication to aHUS that the population pharmacokinetic and pharmacodynamic parameter estimates of aHUS patients were no different from that of PNH patients, and that ravulizumab has already demonstrated an activity comparable to the one of eculizumab in the treatment of adult patients with PNH.[2] The EMA subsequently concluded that comparative efficacy has been substantiated in the adult population (the PNH trial programme did not include paediatric patients as PNH is extremely rare in children).[2]

The aHUS clinical community consulted in the UK were also confident that ravulizumab has similar efficacy and safety to eculizumab.[2, 6]

The assumption of no clinical difference in efficacy and safety between eculizumab and ravulizumab is therefore based on data from a cohort of patients who 'switched' from eculizumab treatment to ravulizumab, sound biological rationale and expert opinion supportive of non-inferiority head-to-head data in the PNH setting, as well as on the lack of statistically significant differences between the treatments observed in the ITC analysis.

B2. Priority question. The ERG considers the submitted model is not sufficiently flexible to consider treatment discontinuation after re-initiation of treatment. As a result, please provide the following:

a. Justification for why the model allows for discontinuation after initial treatment but then assumes lifelong treatment once patients are re-initiated on treatment, i.e., patients are only permitted to discontinue therapy once in the model. Please support this assumption with a review of the literature to identify evidence that could inform the relapse rates after a second or subsequent treatment discontinuation.

As discussed in Section B.3.3.1, Page 117, treatment discontinuation in clinical practice is complex and patient specific. The summary of product characteristics (SmPC) for eculizumab recommends treatment for the patient's lifetime and the SmPC for ravulizumab does not give specific reasons why a patient may discontinue.[32, 33] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines explain that there are no prospective controlled studies which define criteria for discontinuation and makes recommendations based on clinical expert opinion.[34] A more recent publication looking into defining treatment duration for aHUS patients concludes that given the complex and unpredictable nature of aHUS prospective trials are needed to define optimal treatment duration.[35]

The economic model already simplifies the first treatment discontinuation by splitting the reasons patients can discontinue into four categories, defined based on feedback from UK clinical experts. Patients will generally discontinue if they have a confirmed misdiagnosis of aHUS (usually within the first month), have no renal response (usually within the first 3-4 months) or can discontinue for other reasons such as adverse events, patient or physician preference or pregnancy. Discontinuing for renal response is not current clinical practice but is currently being observed in the

SETS study and therefore could impact future treatment discontinuations. The model includes this as a scenario. Given the variation in clinical practice associated with first treatment discontinuation, the uncertainty is greater when considering patients who discontinue a second time.

SETS is the only study which has a formal treatment discontinuation protocol but is still ongoing and therefore no data is available to inform treatment discontinuation patterns. The global aHUS registry, which was initiated in 2012, has recently been used to analyse patient outcomes once they discontinue from eculizumab.[36] Of the 1,794 patients enrolled into the global registry, 151 met the inclusion criteria for the analysis and had discontinued eculizumab after ≥1 month of treatment. From the 151 patients who had discontinued, 30 (19.8%) restarted treatment. No information is provided on how many had a second discontinuation. Using the long-term eculizumab clinical study (C11-003), patient-level data was analysed to review how many patients had multiple treatment discontinuations. Of the 93 patients in the full analysis set (FAS), 42 (45.2%) were marked as having a treatment discontinuation. Of these 42 patients, 21 (50.0%) restarted treatment, then a further 6 discontinued treatment a second time (for reasons other than end of study period). Although this data demonstrates that multiple treatment discontinuations may happen in practice, observed data is limited to 6 patients from the long-term eculizumab study and no data is available to inform what criteria should be met for a patient to discontinue a second time.

The model is currently split into four main health states based on treatment status, each of which are split further into eight subhealth states around aHUS progression. This gives a total of 32 health states in the model and using a two-week cycle length over a maximum of 100 years, the model includes a large amount of information. Adding in another layer of treatment discontinuation would have added additional complexity to the structure, and based on little data and clinical backing, was considered unnecessary. In addition, given that treatment discontinuation patterns are expected to be the same between eculizumab and ravulizumab[6], and no specific data for ravulizumab are available, a simplified assumption keeping patients on treatment for their lifetime once they reinitiate treatment was taken forward within our

submitted analyses. This approach corresponds with the opinion of clinicians on treatment discontinuation in practice.

b. A revised version of the model with sufficient flexibility to model a treatment-relapse disease with greater than one discontinuation, i.e. a model that is not limited to lifelong treatment after re-initiation of treatment. In the absence of sufficient evidence to inform this, please consider whether it is appropriate to assume that the risk of relapse is independent of the number of previous relapses. The ERG believes the model could be further simplified by assuming a constant rate of discontinuation following re-initiation.

As already noted, there are limited data available on frequency and reasons for discontinuation, relapse and treatment re-initiation in clinical practice to inform any change to the model. Alexion consider it inappropriate to assume that the risk of relapse in patients with greater than one discontinuation is independent of the number of previous relapses. Although the data in this area is limited, a recent review article identified the patient's personal medical history as an important risk factor associated with relapse following treatment discontinuation.[35] Data from the French Registry reported that the rate of relapse following eculizumab withdrawal was higher in those who had experienced at least one aHUS episode prior to treatment[37], and similarly the Global aHUS Registry reported higher rates of off-treatment TMA in those with a history of multiple TMA episodes.[12] A recent Dutch study that investigated a restrictive eculizumab treatment strategy implemented a more gradual withdrawal of treatment in patients with previous history of relapse due to perceived higher risk.[38]

Although close monitoring and rapid reintroduction of treatment following TMA relapse post-withdrawal is a consideration for some patients, irreversible renal damage is also a potential risk from repetitive renal flares. The management of a relapse in the ongoing SETS study is to reinitiate eculizumab treatment within 24 hours of presentation, with patients remaining on treatment for the entire of period of follow-up. In addition, a more recent publication looking into defining treatment duration for aHUS patients concludes that given the complex and unpredictable nature of aHUS, prospective trials are needed to define optimal treatment duration.[35] Given the complex and unpredictable nature of aHUS, and the limited data currently

available to inform guidelines related to one discontinuation, it is unlikely that clinical practice of multiple discontinuations will be implemented at this time.

As such, the current model structure is considered appropriate for the current decision problem. Given the complexities of incorporating an additional health-state with sub health states, and possible subsequent relapses and re-treatments, lack of data to inform these transitions and published clinical opinion suggesting that clinical practice is unlikely to incorporate multiple discontinuations the model has not been adapted.

Adverse events

B3. Priority question. The scenario analysis using differential efficacy for chronic kidney disease (CKD) stage is based solely on the ITC analysis that does not consider differential adverse events for ravulizumab and eculizumab (e.g., it does not include the four patients who died during the ALXN1210-aHUS-311trial). Please provide cost-effectiveness results for the ITC scenario that explicitly models the impact of the adverse events (4 deaths for ravulizumab) on mortality.

The base case ITC analysis included three patients who died in the adult non-transplant population, the other patient is included in the adult prior transplant population. One of the three patients had no CKD stage at baseline or post-baseline and discontinued after the first dose of ravulizumab as it was concluded they were ineligible for the trial. This patient died approximately 11 days after discontinuing. As this patient contributed to the overall propensity score weightings, this patient could not be removed without impacting the other weights. Therefore, for the model the subgroup with deaths excluded was used. Given that the deaths in the ravulizumab trial were not deemed related to study drug and the patients who died had significant comorbidities and presented in a critical state, they would have been considered high-risk at presentation and as such would probably not have been treated with complement-inhibitor treatment in UK clinical practice (Document B, Section B.2.10.3, Page 93).[6] Thus, by excluding these patients the results are more likely to represent patients who will be treated in the UK.

Given the similarities between ravulizumab and eculizumab, and ITC results supporting similar efficacy, mortality is not expected to differ between treatment

arms. In addition, given the positive outcomes of eculizumab on mortality, and no reported deaths from NRCTC associated with aHUS or its treatment, it is assumed that patients in the model have the same mortality risk associated with other patients with CKD and no additional risk due to aHUS (see Appendix N.1.2, Page 109).

The transition probabilities calculated from the probit regression model considers transitions between CKD states and does not model deaths explicitly. Due to the relatively few deaths which occurred in the trials, and the fact that the trials were not powered to detect mortality, including it within the ordinal probit models would likely underestimate mortality in the long term (in a time-to-event analysis it would be considered too immature to use data for OS if mortality was 10%). Thus, the trial data and ordinal regression approach were used to model progression of CKD only, while separate data and methodology were used to model mortality. In addition, if mortality has been explicitly modelled "partially" based on the trial data, it could lead to double-counting and challenges with disentangling effects from other data sources used to supplement. Therefore, any patients who no longer have a CKD stage (due to death or loss of follow-up) were censored in the analysis and external sources were used to model patients mortality.

As requested, a scenario has been evaluated which uses the ITC analysis including deaths from the ravulizumab arm which models trial mortality explicitly.

In the ravulizumab 311 trial, the 4 patients all died when in CKD stage 5. Based on the 4 deaths out of the 58 patients in the safety set and mean follow-up of 70.05 weeks, a constant mortality rate was calculated to be 0.204% per model cycle over the model time horizon. In the model, this mortality rate is applied to adult ravulizumab patients in CKD 5. To avoid double counting excess death associated with CKD 5/ESRD, when this scenario is included, the CKD 5 excess death versus general population in the model is not applied to ravulizumab patients.

In the long-term eculizumab trial (C11-003), three deaths were recorded in the long-term and parent studies; two in children under 5 years and 1 in an adult. Similarly to the deaths reported in the ravulizumab trial, none were associated with treatment and the adult and one of the children had discontinued eculizumab prior to their death.[39] As it is unclear at what time point these deaths occurred, eculizumab trial

mortality has not been included in this scenario. Only the deaths occurring in the ravulizumab trial have been incorporated which is bias against ravulizumab. Table 6 presents the cost-effectiveness results using the scenario with ITC including deaths and modelling mortality from the trials explicitly.

Table 6: Cost-effectiveness results – ITC –including deaths and mortality from the ravulizumab trials

Technologies	Total			Incremental			ICER	iNMB
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Ecu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		4,783,703
Rav	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**478,122**	3,443,263

Key: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; iNMB, incremental net monetary benefit; WTP, willingness to pay.
Notes: Adults represent [redacted] of the combined adult and children population.

Health related quality of life

B4. Please clarify whether any data manipulation was required (e.g., handling missing data) for the EQ-5D data collected in each of the ravulizumab and eculizumab clinical trials, and, if so, describe the methods used. On page 128 of Document B, it states that patients who had missing EQ-5D-3L data were removed from the analysis. Please provide a descriptive summary of the level of missing data. In addition, please describe the similarities (or differences) between the characteristics of patients who were excluded due to missing EQ-5D data and patients who were included in the fitted mixed effects model. If missing data were not imputed, please provide justification for not considering imputation methods.

Out of the 1,575 utility records, 125 (8%) were removed from the descriptive summaries and mixed effects models that used data on CKD stage, due to an unknown or missing CKD stage at the date of utility record. One patient in trial C08-003 had 25 records removed because of an unknown CKD stage at time of utility record. This patient had a kidney transplant on day 217 of the study and was subsequently excluded from any further analysis of TMA response and renal function. While utility data was recorded after day 217, no data on CKD stage was available for this patient after day 217, leading to 25 utility records not having an

associated CKD stage at the time of utility record. However, utility and CKD data were used up until day 217 for this patient. The remaining 100 utility records that were removed due to missing CKD stage data were across 73 patients. 67% of these patients only had 1 record removed; 29% of these patients had 2 records removed, and only 4% of patients had 3 records removed. For patients with 1 or 2 missing records, these records were the final utility records available for the patients, and no CKD record for these patients occurred on or after the date of the utility record.

Table 7 describes the characteristics of the patients who had at least one utility record excluded due to missing data compared to characteristics of the overall population. There are no substantial differences between the overall population and those who had missing data.

Table 7: Characteristics of patients who had at least 1 utility record removed due to missing data

Characteristic	Patients with at least 1 utility record removed due to missing data		Characteristics of overall patient population	
	Ravulizumab (n=58 patients, 384 records)	Eculizumab (n=72 patients, 1,191 records)	Ravulizumab (n=58 patients, 384 records)	Eculizumab (n=72 patients, 1,191 records)
Number of records	61 (15.9%)	64 (5.4%)	384 (100%)	1,191 (100%)
Number of patients	45 (83.3%)	29 (40.8%)	58 (100%)	72 (100%)
N patients with 1 record removed 2 records removed 3 records removed 25 records removed	 30 (67%) 14 (31%) 1 (2%) 0 (0%)	 19 (66%) 7 (24%) 2 (7%) 1 (3%)	NA	NA
Mean age (years)	40	36.9	43.0	38.2
Median age (min, max)	37 (19, 74)	31 (21, 69)	40.5 (19, 77)	38.2 (18, 80)
Sex Male Female	 14 (31%) 31 (69%)	 14 (48%) 15 (52%)	 19 (33%) 39 (67%)	 25 (35%) 47 (65%)
On dialysis at baseline Yes	 21 (47%) 24 (53%)	 9 (31%) 20 (69%)	 30 (52%) 28 (48%)	 29 (40%) 43 (60%)

Characteristic	Patients with at least 1 utility record removed due to missing data		Characteristics of overall patient population	
	Ravulizumab (n=58 patients, 384 records)	Eculizumab (n=72 patients, 1,191 records)	Ravulizumab (n=58 patients, 384 records)	Eculizumab (n=72 patients, 1,191 records)
No				
Prior kidney transplant				
Yes	6 (13%)	13 (45%)		
No	39 (87%)	16 (55%)	8 (14%)	24 (33%)
			50 (86%)	48 (67%)
CKD stage at baseline				
Stage 2	3 (7%)	1 (3%)	3 (5%)	2 (3%)
Stage 3	3 (7%)	6 (21%)	3 (5%)	14 (19%)
Stage 4	7 (16%)	4 (14%)	10 (17%)	14 (19%)
Stage 5	31 (69%)	10 (34%)	41 (71%)	33 (46%)
Missing	1 (2%)	8 (28%)	1 (2%)	9 (13%)
Platelet count at baseline				
<150 x 10^9/L	34 (76%)	18 (62%)		
≥150 x 10^9/L	11 (24%)	11 (38%)	46 (79%)	44 (61%)
			12 (21%)	28 (39%)
LDH at baseline				
≤ULN	2 (4%)	11 (38%)	5 (9%)	27 (38%)
>ULN	43 (96%)	18 (62%)	53 (91%)	45 (62%)
eGFR at baseline				
<15	31 (69%)	13 (45%)	41 (71%)	37 (51%)
15-29	8 (18%)	6 (21%)	11 (19%)	16 (22%)
30-44	1 (2%)	8 (28%)	1 (2%)	14 (19%)
45-59	1 (2%)	1 (3%)	1 (2%)	3 (4%)
60-90	3 (7%)	1 (3%)	1 (2%)	2 (3%)
Missing	1 (2%)	0 (0%)	3 (5%)	0 (0%)

Key: CKD, chronic kidney disease; eGFR, estimated globular filtration rate; LDH, Lactate dehydrogenase; ULN, upper limit of normal.

Given these 100 records only made up 6% of the 1,575 utility records (excluding the 25 records from the patient who had a kidney transplant), imputation methods were not considered, and the 1,450 complete records were deemed sufficient to model utility by CKD stage.

As a scenario, we have carried forward the last known observation of CKD stage for these 100 records. The 25 missing records for the patient who had a kidney transplant were not imputed in this scenario, given the number of missing records for this patient was quite large, imputing the last known CKD stage was considered not appropriate and could introduce unknown bias.

This scenario resulted in eight records remaining with unknown or missing CKD stage at the time of utility record. Six of these had missing dates for the utility record and could not be matched to any CKD stage records. The remaining two occurred before the baseline record, and no associated CKD stage could be found for those dates. The last observed value carried forward (LOCF) scenario resulted in model coefficients greatly similar to the analysis currently used in the economic model (Table 8). Given this similarity, we believe the current analysis is sufficient to model utility. More complex methods for data imputation were not considered, given the amount of missing data is small.

Table 8: Model coefficients for mixed effects regression: analysis excluding missing records vs LOCF scenario

Current analysis		LOCF scenario	
Intercept	0.777	Intercept	0.793
Baseline utility	0.244	Baseline utility	0.231
CKD stage 3	-0.052	CKD stage 3	-0.060
CKD stage 4	-0.154	CKD stage 4	-0.155
CKD stage 5	-0.212	CKD stage 5	-0.223
Key: CKD, Chronic Kidney Disease; LOCF, last observed value carried forward			

Treatment costs

B5. Priority question. In HST1, the committee concluded that it "had not been presented with sufficient justification for the high cost per patient of eculizumab in light of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition". Despite the lower cost of ravulizumab compared to eculizumab, its cost per patient is £258,286 in the first year (based on

weighting of adults and children). Please comment on what evidence have been provided in this submission to justify the high costs of ravulizumab.

The prices of Alexion's medicines, including ravulizumab, take into consideration the life-changing value they bring to patients, their families, healthcare systems and society, the rarity and medical need of the diseases they treat, and the ongoing investments required to ensure continued discovery and development of new innovative medicines for people with rare and ultra-rare diseases.

We believe we have presented a robust package of clinical and pharmacoeconomic evidence in the CS demonstrating the additional value that ravulizumab can provide to patients and their families or carers. From a clinical perspective, ravulizumab offers immediate, complete and sustained complement inhibition with no unexpected safety concerns while reducing treatment burden with only six or seven infusions per year compared with 26 infusions for eculizumab. The pharmacoeconomic analyses presented in the company submission include a cost minimisation analysis, a cost utility analysis and budget impact analysis for the 5 years of ravulizumab use compared with eculizumab based on the accepted PAS. The cost minimisation analysis demonstrates that ravulizumab is cost saving compared with eculizumab, reducing treatment costs by [redacted]% over a patient's life-time (a total saving of [redacted] per patient). The cost utility analysis yields an ICER that sits within the South-West quadrant of the cost-effectiveness plane and remains well above the threshold to consider eculizumab more cost-effective than ravulizumab (ICER [redacted]). The budget impact analysis shows that use of ravulizumab over eculizumab could save NHS England as much as [redacted] over the first five years.

The price for ravulizumab reflects Alexion's globally sustainable pricing strategy to drive innovation and deliver life-changing therapies to patients with rare diseases. Furthermore, to enhance the value offered by ravulizumab in aHUS, and to facilitate access to patients, we have offered a patient access scheme with a [redacted] discount over the list price. [redacted]

B6. In the paediatric model, please clarify why the weight distribution of children once they reach the age of 18 years is different from the weight distribution assumed

for adults. In addition, please implement an additional scenario analysis where the paediatric patients who become adults follow the adult weight distribution (i.e., 23.5% assumed to weigh between 40 kg and 60 kg, 69.7% between 60 kg and 100 kg, and 6.9% above 100 kg).

In the model, the weight and age distributions are based on patient level-data from the trials thus, patients begin the model at various ages (ranging from <1 year to 17 years). Children turn 18 at different time points therefore ensuring that the weight distribution estimated for children over the model time horizon transitions to the adult distribution was not possible without applying an adjustment at a fixed time point which disregards the individual ages of the population. The alternative approach taken for the model was to try and ensure the mean weight of the paediatric population did not greatly exceed the mean weight of the adult population. Therefore, children's weight increases until they either turn 18 or the mean weight has reached the mean weight of the adult population. This results in the following distributions presented in Table 9 and resulted in a slightly heavier adult paediatric population compared to the modelled adult population. However, this only increases the costs of ravulizumab given the eculizumab dose for patients over 40kg is the same and was therefore considered conservative.

Table 9: Patient modelled weight distribution

Weight range (kg)	Adult population	Paediatric population (when reach adults)
≥ 10 to < 20	[redacted]	[redacted]
≥ 20 to < 30	[redacted]	[redacted]
≥ 30 to < 40	[redacted]	[redacted]
≥ 40 to < 60	[redacted]	[redacted]
≥ 60 to < 100	[redacted]	[redacted]
≥ 100	[redacted]	[redacted]
Mean weight (kg)	[redacted]	[redacted]

In order to merge the children's weight distribution to the adult weight distribution a scenario has been added to the model which adjusts the weight buckets at the point the weight distribution overtakes the adult weight distribution. In the model, this switch can be found in the 'Inputs – General Disease Tx' sheet, row 166. At this time point, the adjustment changes the weight distribution to follow the adult weight

distribution. Figure 2 demonstrates the paediatric weight adjustment and Table 10 presents the cost-minimisation results when this adjustment is applied in the model. This results in a slightly increased cost-saving for ravulizumab.

Figure 2: Adjusted paediatric weight distribution versus adult weight distribution

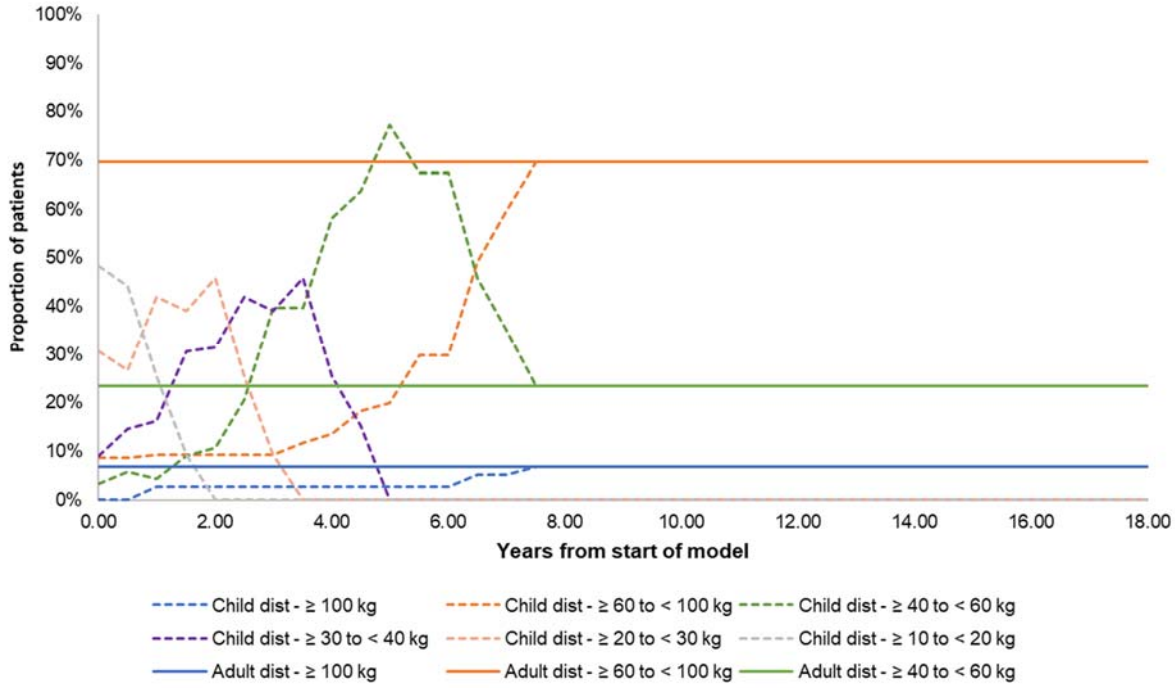


Table 10: Results after adjusting the paediatrics weight distribution

Costs	Eculizumab	Ravulizumab
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
Key: PAS, patient access scheme.		

B7. On page 96 of Document B it states that the potential loss of earnings associated with eculizumab infusions is estimated to be approximately £728 per year on average, while equivalent loss earnings for ravulizumab is approximately £375 per year on average. Please clarify how these estimates were calculated in light of the quadruple frequency of eculizumab infusions in the maintenance dose period compared with ravulizumab.

The potential loss of earnings was estimated with a work productivity calculator that considered multiple factors including treatment setting. A simplified calculation that

considers the number of infusions, the average minutes per infusion, and the average preparation and monitoring time for both treatments is provided in Table 11.

As can be seen from this simplified calculation, the main reason the loss of earnings ratios are not directly correlated with the infusion frequency ratio is the extended infusion time for ravulizumab. It should be noted that this infusion time is reduced with the 100 mg/mL vial sizes that will be launched in the UK and this results in a reduced loss of earnings with ravulizumab and thus a bigger difference in loss of earnings between ravulizumab and eculizumab (Table 11).

Table 11: Simple loss of earnings calculation

	Number of infusions per year	Minutes per infusion[a]	Preparation & monitoring time[b]	Hours per year lost to infusions[c]	Loss of earnings[d]
Eculizumab maintenance dosing	26	35	77.5	48.75	£731.25
Ravulizumab maintenance dosing (10 mg/mL vial)	6.5	130	90	23.83	£357.50
Ravulizumab maintenance dosing (100 mg/mL vial)	6.5	42.5	90	14.35	£215.31
Notes: [a], average of the recommended infusion times from the summary of product characteristics; [b], preparation time reported as 15-20 minutes for eculizumab by clinical experts and extended to 30 minutes for ravulizumab acknowledging the reduced familiarity. Monitoring time reported as 60 minutes for both treatments; [c], calculated as (number of infusions per year x minutes per infusion) + (number of infusions per year x preparation & monitoring time) converted to hours; [d], calculated as hours per year lost to infusions x average hourly wage of £15[40]					

Model worksheets

B8. Priority question. Please provide details about the formula that is used to calculate the '% discount over time' implemented in columns O and P of the 'Calc-Payoff' worksheet in the model (e.g., how it was derived). In addition, please explain how the formula that is implemented in the model relates to the formula provided in section B.3.5.1.7 of Document B, page 142.

The formula used to calculate the % discount over time calculates the discount rate accrued using the area under the exponential curve between two discrete time

points. First the instantaneous discount rate (iDR) was calculated from the annual discount rate:

$$iDR = \ln(1 + DR)$$

Using the iDR, the discounted number of life-years between two discrete time points could then be calculated. The formula presented in Document B, Section B.3.5.1.7, page 142, has been re-written below to be consistent with the formula used in the model (using the correct format to write up exponential equations).

$$Discounted\ number\ of\ years = \frac{e^{(t_{new\ event} - iDR)} - e^{(t_{previous\ event} - iDR)}}{-iDR}$$

$t_{previous\ event}$ represents the starting time of re-treatment and $t_{new\ event}$ represents the end time of re-retreatment (start time + duration of retreatment). In the model, this is then divided by the duration of re-treatment ($t_{new\ event}$ - $t_{previous\ event}$) to give the total discount rate. This reflects the equation used in the model to calculate the discount rate at each time point (see 'Calc – payoff' sheet, columns O and P).

The discounting formula can be derived as follows, where $\frac{1}{(\ln(1+DR))^t}$ is the formula for continuous discounting and $\ln(1.035)$ is the iDR (based on 3.5% discount):

$$\int_{t_{previous\ event}}^{t_{new\ event}} \frac{1}{(\ln(1.035))^t} dt$$

$$= \int_{t_{previous\ event}}^{t_{new\ event}} (\ln(1.035))^{-t} dt$$

$$= \left[\frac{(\ln(1.035))^{-t}}{\ln(\ln(1.035))}\right]_{t_{new\ event}}^{t_{previous\ event}}$$

using $\int a^x dx = \frac{a^x}{\ln(a)} + c$.

Taking exponentials gives:

$$= \left[\frac{\exp(\ln(1.035))^{-t}}{\exp(\ln(\ln(1.035)))}\right]_{t_{new\ event}}^{t_{previous\ event}}$$

$$= \left[\frac{\exp\left(-\ln(1.035) \times t\right)}{\ln\left(1.035\right)}\right]_{t_{new\ event}}^{t_{previous\ event}}$$

using the rules of exponentials where $\exp(\ln(x)) = x$ and $\exp(a^b) = \exp\left(a \times b\right)$. Therefore, the formula for calculating discounted number of years (using area under the curve) is:

$$AUC = \frac{\exp\left(-\ln(1.035) \times\ t_{new\ event}\right)}{-\ln\left(1.035\right)} - \frac{\exp\left(-\ln(1.035) \times t_{previous\ event}\right)}{-\ln\left(1.035\right)}$$

The discount rate is then divided by the duration between the two time points:

$$Discount\ rate = \frac{AUC}{t_{previous\ event} - t_{new\ event}}$$

B9. Please specify the name of the macro that implements the equation of Figure 10 page 108 of Appendix B to derive the transition probabilities within the model from the probit regression coefficients.

The macro named *'PF_Automation'* within the module *'PF_Automate'* contains the calculations to derive the transition probabilities. The module named *'UDFunctions'* includes a user defined function used for these calculations (*'CalcProb')* which implements the equation of Figure 10, page 108 of Appendix N.

B10. Please clarify why a standard error of 10% of the mean was used to fit a statistical distribution to all the parameters used in the model. In addition, please provide an updated model with appropriate standard errors used where 95% confidence intervals were available, e.g., 95% confidence interval is reported for the 'decreased burden of treatment' utility gain parameter in section B.2.12. of Document B, page 95.

Confidence intervals and standard errors were taken from the literature where available. If these were not presented, then the standard error was assumed to be 10% of the mean and confidence intervals calculated based on the assigned

distribution (see Appendix Q, Page 152). This is a standard assumption used in cost-effectiveness models if the uncertainty information is not available.

The standard errors and confidence intervals for all model parameters have been reviewed. Where possible standard errors have now been estimated based on the confidence interval (if reported) and distribution assigned. As part of this review some confidence intervals have been updated based upon the information available. Table 12 shows the specific parameters which have been updated in the revised model and amended values. Figure 3 presents the updated tornado plot from the one-way sensitivity analysis and Figure 4 presents the updated incremental cost distribution from the probabilistic sensitivity analysis. The key drivers have remained the same in the model and the uncertainty remains consistent with that previously presented.

Table 12: Parameter distribution updates

Parameter	Mean	Distribution	Previous model value/assumption			New value/assumption			Source	Reference and explanation for amended value
			CI (Lower Bound)	CI (Upper Bound)	SE	CI (Lower Bound)	CI (Upper Bound)	SE		
CKD stage 0-2 excess mortality rate (adults)**	2.2	Log normal	2.1	2.4	0.22*	Unchanged	Unchanged	0.03	Erikson et al, 2006[41]	Calculated SE from confidence intervals using log normal distribution
CKD stage 3a-3b excess mortality rate (adults)	2.2	Log normal	2.1	2.4	0.22*	Unchanged	Unchanged	0.03	Erikson et al, 2006[41]	
CKD stage 4 excess mortality rate (adults)	2.56	Log normal	1.75	3.75	0.26*	Unchanged	Unchanged	0.19	Sud et al, 2016[42]	
CKD stage 0-2 excess mortality rate (children)	3.1	Log normal	2.5	3.9	0.31*	Unchanged	Unchanged	0.11	Erikson et al, 2006[41]	
CKD stage 3a-3b excess mortality rate (children)	3.1	Log normal	2.5	3.9	0.31*	Unchanged	Unchanged	0.11	Erikson et al, 2006[41]	
CKD stage 4 excess mortality rate (children)	2.56	Log normal	1.75	3.75	0.26*	Unchanged	Unchanged	0.19	Sud et al, 2016[42]	
Baseline utility	0.52	Beta	0.44	0.60	0.04	0.44	0.61	Unchanged	Utility analysis from the clinical trials	
Relapse health-utility decrement (annual) - Van de Brand	0.055	Beta	0.045	0.066	0.0055*	0.01	0.11	Unchanged	van den Brand et al, 2017[43]	Not the 95% CI, but the range given from clinical opinion
Decreased burden of treatment (10mg/mL)	0.007	Beta	-0.001	0.015	0.0007*	Unchanged	Unchanged	0.0041	Alexion. DCE UK. Data on file[44]	Calculated SE assuming normal distribution
Decreased burden of treatment (100mg/mL)	0.013	Beta	0.007	0.02	0.0013*	Unchanged	Unchanged	0.0031	Alexion. DCE UK. Data on file[44]	

Parameter	Mean	Distribution	Previous model value/assumption			New value/assumption			Source	Reference and explanation for amended value
			CI (Lower Bound)	CI (Upper Bound)	SE	CI (Lower Bound)	CI (Upper Bound)	SE		
Resource utilization: CKD 0 – 2	17.4	Normal	13.95	20.75	1.74*	14.86	19.89	1.3	Kent et al, 2011[45]	Confidence intervals reported in Kent et al 2011. [45] SE calculated assuming normal distribution
Resource utilization: CKD 3a - 3b	17.4	Normal	13.95	20.75	1.74*	14.86	19.89	1.3	Kent et al, 2011[45]	
Resource utilization: CKD 4	16.9	Normal	13.61	20.24	1.69*	14.77	19.12	1.1	Kent et al, 2011[45]	
Resource utilization: CKD 5	22.6	Normal	18.18	27.04	2.26*	19.33	25.92	1.7	Kent et al, 2011[45]	
Resource utilization: Transplant	1059.4	Normal	851.75	1267.02	105.94*	1034.62	1084.18	12.6	Kent et al, 2011[45]	
Resource utilization: Transplant Success	49.4	Normal	39.74	59.12	4.94*	42.11	56.75	3.7	Kent et al, 2011[45]	
Cost of dialysis (2-week value)	1004.4	Normal	807.57	1201.3	100.44*	801.79	833.31	103.4	Kent et al, 2011[45]	

Key: CI, Confidence Interval; SE, Standard Error

Note: *SE assumed to be 10% of the mean as it was unreported in the literature. **CI only used for eculizumab arm, this has now been corrected

Figure 3: Updated incremental costs tornado plot

Key: CKD, chronic kidney disease; ECU, eculizumab; ESRD, end-stage renal disease; PAS, patient access scheme.

Figure 4: Incremental cost distribution (1,000 PSA runs)

Key: PSA, probabilistic sensitivity analysis

Inconsistencies between economic model and reported values

B11. The ERG noted some discrepancies between the results reported in Table 52, page 153 of Document B and the model outputs when re-running these deterministic analyses. Examples of the discrepancies are shown in the Table below:

Scenario category	Base case	Scenario	Incremental costs (£) provided in SensitivityAnalysis sheet	Incremental cost (£) obtained by rerunning analysis	Difference found
Base case			[redacted]	[redacted]	No
Time horizon	100 years	20 years	[redacted]	[redacted]	Yes
		50 years	[redacted]	[redacted]	Yes
		70 years	[redacted]	[redacted]	Yes
Efficacy comes from naïve comparison*			[redacted]	[redacted]	Yes
Treatment discontinuation	General discontinuation using pooled ITC	aHUS registry	[redacted]	[redacted]	Yes
	Discontinuation due to renal recovery excluded	65% discontinue at 6 months due to renal recovery	[redacted]	[redacted]	Yes

Please explain the reason(s) for these apparent discrepancies.

The discrepancies highlighted by the ERG have been reviewed and an explanation of differences have been provided in Table 13. The revised model includes a re-run of the scenario analysis which is now correct.

Table 13: Explanation of the discrepancies between company scenario analysis and ERG analysis

Scenario category	Base case	Scenario	Correct value	Explanation
Base case			[redacted]	
Time horizon	100 years	20 years	[redacted]	Error found in PF_automate macro which produces the transition probabilities. This was linking to the time horizon
		50 years	[redacted]	
		70 years	[redacted]	

Scenario category	Base case	Scenario	Correct value	Explanation
				cell and not using the full length of the patient flow sheets if the time horizon was manually changed. This did not seem to impact the scenario analysis run. This has now been corrected in the model such that manually changing the time horizon and updating results match the results from the scenario analysis.
Efficacy	ITC	Naive comparison	[redacted]	The above error had an impact on the next scenario run. This has now been corrected with the above fix.
Treatment discontinuation	General discontinuation using pooled ITC	aHUS registry	[redacted]	As the aHUS registry data includes all possible reasons for discontinuing treatment, when this scenario is run the other treatment discontinuations (mis diagnosis and no renal response) included in the model are switched off. Sheets 'Inputs - General Disease Tx' cells F123 & F125
	Discontinuation due to renal recovery excluded	65% discontinue at 6 months due to renal recovery	[redacted]	This result is correct. When the switch for discontinuation due to renal response is considered in the model (Sheets 'Inputs - General Disease Tx' cells F130), the results are consistent with those presented Table 52.

Section C: Textual clarification and additional points

C1. Document B, page 94, states that: "Extension Periods of ALXN1210-aHUS-311 and ALXN1210-aHUS-312 are ongoing with further data expected towards the end

of Q1 2021.” Does the company plan to present longer-term clinical efficacy and safety data, and if so, when?.

As discussed during the Clarification TC, longer-term 104-week clinical efficacy and safety data are expected to be available towards the end of Q1 2021. These data will not be available in time to be considered as part of this submission.

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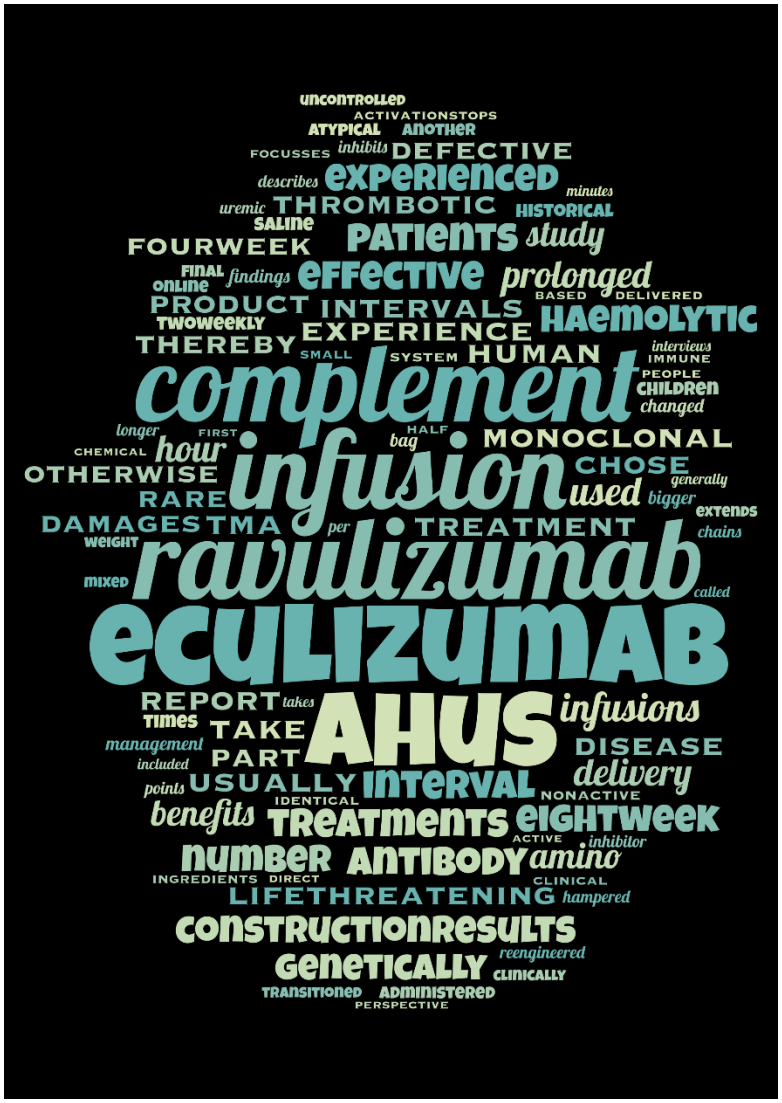

A REPORT ON THE COMPARATIVE EXPERIENCES AND EXPECTATIONS OF THE IMPACT ON aHUS PATIENTS FOLLOWING A TRANSITION FROM ECULIZUMAB TO RAVULIZUMAB FOR THE TREATMENT OF aHUS

Version: 4/10/2020

aHUS alliance Global Action

1.Introduction

Atypical Haemolytic Uremic Syndrome, or aHUS, is an exceedingly rare life-threatening thrombotic microangiopathy, or TMA, which damages the kidneys in particular because of uncontrolled activation of a genetically defective, or otherwise hampered, part of the innate immune system called Complement.

Since 2011, when it was first licensed to be used, the most clinically effective treatment of aHUS has been a human monoclonal antibody called eculizumab. It inhibits unregulated Complement activation and stops TMA activity. It is delivered to patients by infusion of weight related doses, usually at two-weekly intervals. Infusion access is made via an implanted port, or direct into a vein or into a fistula for those patients who have been on haemodialysis (sometimes needled by patients themselves).

Another Complement inhibitor called ravulizumab has been developed by the same manufacturer. This too is a human monoclonal antibody identical to eculizumab but re-engineered with changes to four points in the amino acids chains of its chemical construction. The modifications result in a prolonged active half-life of the effective ingredient and therefore extends the interval between infusions. Maintenance dose infusions are usually administered at eight-week intervals for adults and a four-week interval for small children.

The non-active ingredients included in the final product are the same for both eculizumab and ravulizumab. Ravulizumab is, however, mixed into a bigger bag of saline for infusion than that used for eculizumab because of the higher number of vials of ravulizumab used per infusion. An infusion of ravulizumab can take more than three to five times longer than for eculizumab, which generally took thirty minutes to one hour.

This report describes the impacts experienced by aHUS patients who have transitioned from eculizumab to ravulizumab treatment as well as the impact expectations of aHUS patients who are yet to transition from eculizumab.

The specific focus of the study is the delivery of both treatments rather than their clinical benefits compared with no treatment or a historical perspective on how disease management has changed over time. Participants weren't asked about other treatments which they may be receiving.

2. Methods Used

The research was conducted between 3 August 2020 and 12 September 2020.
There was no conflict of interest amongst any of the participants contributing to the study.

The method used was chosen because it was impractical to conduct extended and recorded face to face interviews in the time available. Interviewees felt comfortable with writing and talking about their experience.

The study report is therefore based on the results from 13 online interviews with people with direct experience of both treatments and 5 online interviews with patients with experience of eculizumab only. No volunteers with experience of ravulizumab only participated in the study.

Participants volunteered to give statements following a social media call on 3rd August 2020 via the aHUS alliance Global Action's website, Facebook Page and in a closed aHUS Families Facebook Group, for patients with experience of both eculizumab and ravulizumab use. Although though the call for volunteers was to global aHUS patients, only patients from the USA offered to participate. The characteristics and time on both treatments of the participants are given in Table 1. The group's average time on eculizumab had been 4 years 5 months and 7 months on ravulizumab.

Table 1: Characteristics and treatment duration of experienced participants

Participant's Identifier	Participant's Role	Gender of patient	Age at August 2020	Time on eculizumab	Start month	Time on ravulizumab
A	Patient	Female	NK	NK	NK	NK
B*	Patient	Female	NK	4y 11m	5/20	4m
C	Patient	Female	46	9m	4/20	5m
D	Patient	Female	68	2y	1/20	8m
E	Patient	Female	51	6y 6m	12/19	9m
F	Carer	Male	11	10y 5m	2/20	7m
G*	Carer	Female	13	6y	11/19	10m
H	Patient	Female	47	6y	1/20	8m
I	Carer	Male	13	5y 6m	12/19	9m
J	Patient	Female	62	3y	1/20	8m
K	Patient	Female	38	3y	4/20	5m
L*	Patient/Carer	Male	23	1y 2m	5/20	4m
M	Patient	Male	22	4y 6m	12/19	9m

*transplant patient y -years m-months

The US Food and Drugs Agency (FDA) approved the use of ravulizumab on 18th October 2019 and so, by the time of this study, all experience of ravulizumab following transition is limited to less than a year, and to between 2 to 5 treatment cycles. No respondents had participated in any ravulizumab trial.

Participants provided some initial information when offering to volunteer, but all were written to with a further explanation of the purpose of the research, and what was expected of them, and to give assurance that information would be kept in confidence and participants anonymity would be maintained. Each was asked to write freely about what mattered to them in the transition, but some topic areas were suggested for them to think about. A follow up individual meeting by Zoom was offered and taken up by seven of the participants to clarify statements made and add further experience comments.

Each was asked about their length of time on both therapies. Details about their aHUS onset experience and recovery were not asked for but three volunteers mentioned that the patient had a kidney transplant.

For volunteers with experience of eculizumab only, known UK aHUS patients on eculizumab were contacted by telephone/messaging, and told about the research being done and asked to volunteer to participate. None of them had experience of using ravulizumab and each had little knowledge of the new technology other than the time for infusion was longer than for eculizumab, but so too was the interval between infusions. The characteristics of the UK eculizumab only participants are given in Table 2. The group's average time on eculizumab has been 6 years 2 months,

Table 2. Characteristics and treatment duration of UK participants

Participant's Identifier	Participant's Role	Gender of Patient	Age at August 2020	Time on Eculizumab
A	Patient	Female	28	5y 6m
B*	Patient	Female	46	5y 10m
C*	Patient	Female	51	5y 2m
D	Patient	Female	34	10y 4m
E	Patient	Male	37	4y 3m

* transplant y-years m-months

In an email exchange volunteers were asked to write freely about what mattered to them in a potential transition from eculizumab, but some topic areas were suggested for them to think about. Each was asked about their length of time on eculizumab. Details about their aHUS onset experience and recovery were not asked for but two participants mentioned that they had a kidney transplant.

The responses from both the "experienced" and "expectant" participants were pasted to a summary document for analysis. Themes were identified and comparable and contrasting views of participants summarised. This work was done by the Trustees of aHUS alliance Global Action.

The results from the experienced group are given in Section A and the expectant group in Section B. In both sections direct quotes from interviewees appear *in italic* and are attributed to the role of the interviewee; patient or carer, as stated in the relevant Tables 1 and 2.

3. Results

Section A - Impact statements from patients who have transitioned from eculizumab to ravulizumab treatment.

A1. Transition process

The earliest transition from eculizumab to ravulizumab occurred within a month of FDA's approval of ravulizumab on 18 October 2019. Seven respondents said they had transitioned by the following January.

From those who disclosed it, the impetus to change mostly came from the patients themselves. They reported that they had been watching and waiting for FDA approval

and had sought the move to ravulizumab when it became possible. For others it was their clinician who recommended a move. Several stated that their insurance providers were eager for them to change to ravulizumab treatment. Overall patients were keen to try it and generally were relaxed about doing so.

My doctor pushed for my switch to ravulizumab, but also my insurance company did as well, I'm assuming because it is less expensive. (Patient C)

With the FDA approval of Ravulizumab in October 2019, I requested the changeover immediately, but it was not cleared until January 2020 (Patient D)

Once the FDA approved ravulizumab, I contacted my doctor as well as the employer providing my insurance, because they started directly paying for my eculizumab treatment when their re-insurance denied coverage after a year. My doctor approved the change… (*Patient* E)

My son's doctor did first mention the medicine to us and started the process of insurance approval once it was FDA approved. It took about 3 months once the new medicine was FDA approved for both the hospital board to approve getting the medicine and insurance to preapprove the new medicine *(*Carer Patient F)

The transition was our choice. As soon as we heard of the FDA approval, I contacted our son's physician to begin the process. Our son was the first non-clinical trial paediatric patient in the US to transition (Carer Patient I)

I learned about the new drug being approved from a nurse in the infusion room…. so, I told the doctors I wanted to move to the new drug… insurance approved, and we moved (Patient J)

My doctors told me about ravulizumab so deciding to do it was nothing too crazy, whatever if it's better. (Patient L)

Once approved, the date for the transition protocol to be enacted was set. Two respondents reported some problems with meeting due dates but most reported that the move went to plan with no logistical issues. One mentioned the role played by their "case manager" in helping coordination.

My case manager was vital in coordination of many aspects between doctors, suppliers, facilities, and new nursing company (Patient E)

I started in April of 2020 I believe...then got off a week or so because of a pharmacy mistake (Patient K)

A2. Infusion Process

Two weeks after the last eculizumab infusion a loading dose of ravulizumab is administered. After a further two weeks the first maintenance dose begins and is followed up 8 weeks later and then so on. All respondents reported being on 8-week intervals between doses. No respondent commented on the volume of ravulizumab they were prescribed. On prompting at interview, two respondents reported that 10 and 11 vials of ravulizumab were prescribed according to their weight. (Note:

compared with 16 vials of eculizumab for four treatment cycles over an eight-week period).

The increased length of the time taken over each infusion was mentioned because it was considerably more than for eculizumab, typically 2 to 5 hours, compared with 30 to 60 minutes reported for each eculizumab infusion. So, it is only marginally more than the aggregate time for four separate eculizumab infusions in eight weeks. Patients saw an advantageous quality of life trade-off between having longer infusions and gaining a greater interval between infusions.

Participants reported that not having to attend for infusions every two weeks was a major benefit. Apart from the time gained to do other things, they mentioned how fewer infusions brought a physical and mental relief to the burden of treatment and made life easier for them.

One eculizumab home infusion patient reported a reversion to infusion centre practice for the first dose of ravulizumab so that any reaction could be monitored.

One carer mentioned that her son's access port has been removed to avoid unnecessary hospital visits for line flushing between infusions. Another carer of a patient with a transplant reported her daughter's port was retained for transplant monitoring procedures.

Another respondent reported that the loading dose of ravulizumab followed soon after an Ileostomy operation. The patient felt poorly at the time, with headaches and fatigue, but whether these were attributable to surgical recovery or ravulizumab was unclear.

…***Benefit from longer time in between infusion, thus giving my veins a res*t.** (Patient C)

My first treatment was delivered at my prior infusion facility to watch for reactions then returned to home infusion. (Patient E)

My son has been on eculizumab for all but 4 months of his life and is used to having infusions. Initially he was apprehensive about the extended infusion time but quickly adjusted when he realised it gave him more permitted time on his iPad. ***He had his port removed to avoid the need for flushing between 8-week infusions.*** (Carer Patient F)

I had a surgery to make my ileostomy permanent mid-December then transitioned to ravulizumab the first week of January. The recovery from surgery was more difficult than expected, but the team felt I should still transition in January. I felt poorly but I think that was from surgery more than the new med. I'd say the headaches and fatigue were worse. (Patient H)

The frequency of every 8 weeks has changed patients mental thinking. Going every 8 weeks, it is not so "in your face". (Carer Patient I)

While the infusion is longer, anywhere from 2-5 hours, having 8 weeks to live my life without thinking about the logistics of my next infusion is so freeing. (Patient M)

A3. Efficacy of the Technologies

Most respondents were confident that ravulizumab would be as effective for treating their aHUS as eculizumab had been.

My husband and I saw detailed data on the upcoming ravulizumab and were convinced it was as effective as eculizumab, particularly at keeping complement C5 shut down for the full 8 weeks in over 99% of cases (Patient E)

Several respondents mentioned that their blood results showed little difference following transition, with one respondent reporting a slight improvement after ravulizumab treatment. One patient, who transitioned, immediately following an operation, reported that the clinician had undertaken weekly blood tests in between infusions. Another respondent mentioned that the CH50 blood test was not available for ravulizumab treatment which raised her concern about monitoring efficacy.

The doctor says his labs look great so far and indications are good that the drug is doing well. (Carer Patient F)

My bloodwork has been monitored more closely than before… my clinician decided to take weekly bloods after the early infusions but phased them out over time…ravulizumab is proving to be just as stable as with eculizumab. (Patient H)

…there seems to be a lack of available blood testing to analyse complement blockade in ravulizumab, compared to CH50 with eculizumab. (Patient I)

***Since January, all my lab numbers remain intact*.** (Patient J)

Eculizumab cured all aHUS related health issues and ravulizumab does the same….my blood tests normalized after my initial diagnosis and have remained normal while I've been on eculizumab and ravulizumab. (Patient M)

A4. Side Effects

One respondent reported a side effect from ravulizumab so serious that a reversion to eculizumab was needed. Full details of the reason for the reaction were not provided. As this was the only comment made by the respondent it is not known whether this was reaction to the re-engineered eculizumab, the change in infusion practice, or some breach of transition protocol affecting trough dose.

I went from long term eculizumab to ravulizumab ...had side effects on ravulizumab and I'm now back on eculizumab (Patient A)

Respondents' comments about other side effects were mixed. Some reported that they had no side effects with both eculizumab and ravulizumab; or the side effects were similar from each drug but limited to the infusion day or the day after. The most frequently cited side effects being a regular transitory headache and fatigue in the days following each infusion. Others mentioned included mild joint pain, sore throat, numbness in nasal/sinus area, pain at end of fingers/toes. Where asked, no patient regarded the side effects as debilitating. A small number of respondents felt their side

effects were less after an infusion following ravulizumab transition. One respondent considered that the same side effects after treatment were stronger. Another who experienced a reaction to ravulizumab infusion found slowing down the rate of infusion improved matters. Although not leading to a reversion to eculizumab yet, one respondent felt that the bloating and an inability to lose weight while on ravulizumab is making her think about going back to eculizumab treatment.

***The side effects I experience seem to be a little stronger than with the eculizumab. They are, tiredness, (3-4 days after infusion) more intense joint pain, sore throat, and headache*.** (Patient C)

I had no reactions or side effects at any point on ravulizumab (or on eculizumab) (Patient E)

My son has had no obvious side effects with either medicine (Carer Patient F)

After my daughters first infusion she had an overall feeling of not feeling well, mostly body aches, so we decided to pre-treat with painkiller. That had helped and she really has had no other side effects (Carer Patient G)

I have not experienced any side effects that I didn't have with eculizumab. I think I have fewer headaches and less fatigue now than I did with the eculizumab. (Patient H)

I still have had no side effects from ravulizumab (Patient J)

*…**with my inability to lose weight and the bloating the ravulizumab is causing, I really don't know if I want to stay on it.*** (Patient K)

I feel tired and "not so good" on the day of the infusion and the next day and then I am ok again. (Patient L)

I have had a minor complication, and I never had issues with eculizumab. With ravulizumab the manufacturer recommends providers infuse over 2 hours. Unfortunately, for some reason, my body couldn't handle the drug at that rate, and I had a bit of a reaction the first time I used it. I've since slowed the infusion to 4 hours which I've been able to handle with no complications. (Patient M)

No respondent mentioned any concern about the major side effect from both drugs, i.e. the risk of a meningococcal infections. This perhaps indicates that they thought that any mitigating action taken for eculizumab would apply to ravulizumab too.

A5. Work, School, and Other Activities

Apart from a physical and mental relief from going through the infusion process less frequently, all respondents remaining on ravulizumab refer to the longer intervals as a key benefit, a "game changer". Respondents appreciated and made use of the new "freedom" it gave. The benefits are also felt by carers of patients.

…gives me more freedom because I don't have to worry about scheduling infusions as often… I would say that my day to day life has improved because

of the longer time in between infusions. I am able to plan more activities, trips, etc. (Patient C)

Ravulizumab has certainly helped improve my lifestyle with having six versus twenty six infusions over a year period… my family live in Thailand and a two weekly infusion cycle, unless special carriage of properly stored eculizumab vials is arranged for away from home infusion, limits time I can spend there on visits. Ravulizumab improves my freedom to travel and stay longer*.* (Patient D)

The telling life story was that for the first time in 6 years, I didn't have to schedule an infusion during the holidays! Or arrange my vacation around it. (Patient E)

The time between infusions is a game changer as far as missed school for my son and missed work for myself*.* (Carer Patient F)

… as a nurse missing work as often as I did with eculizumab treatment caused me stress, that it might affect my salary status…ravulizumab has saved me a lot of lost work time, and less use of my precious PTO (paid time off) time … (Patient H)

Missing school once every other week was challenging (especially at higher grade level with multiple teachers). Infusion Center is 2 hours (100 miles) from home- 4 hours travel time, plus fuel and meals… we would also be able to spend more time at our holiday home on vacation as we will not need to return for infusion (Carer Patient I)

…***with not having to plan my entire life around every other Wednesday for medicine is a huge advantage.*** (Patient J)

I wanted to switch for the convenience really. I work full time, plus my husband and I have 3 boys to raise (Patient K)

I would say he has more time for his favourite pastimes, walking and fishing as well as for his full-time job.... we even went on vacation last month to Arizona, 12 hours from here, that is something he would not have done on eculizumab, to go so far away from his home base and treatment (Carer Patient L)

Eculizumab ruled my life. I couldn't study abroad like the typical undergrad, since I needed to coordinate insurance, doctor's care, and eculizumab infusions every two weeks. My insurance company said they would cover two "grace" infusions abroad a year, but that would only allow me to spend a maximum of 6 weeks out of the country. The typical college study abroad program is 5-6 months. (Patient M)

A6. General health

No respondent mentioned the state of their, or their child's, general health but, when asked, they described it as "excellent" and transitioning to ravulizumab made no noticeable difference to that status.

… I feel so much better I have begun training to do a triathlon. (Patient H)

It is like my illness was a dream, unreal, because I feel so well on both drugs, like I was before it happened. (Patient J)

A7. Expense

A small number of respondents commented on the reduced cost of treatment they had observed, not just because of a lower price and fewer vials of ravulizumab needed at their weight, but from the savings also accrued due to less frequent infusion centre use and travel for treatment.

… and the health coverage provider told me it would save them 30% in overall costs. (Patient E)

Based on the figures I see from my insurance company; one other benefit is that it appears that ravulizumab infusions will cost much less on year than eculizumab did. (Patient J)

A8. Other Issues

One respondent reported that she had experienced a COVID 19 infection earlier in August 2020. The course of the disease, although typically symptomatic, ended quickly and she was in quarantine working from home. There had been no problems from being on ravulizumab.

Other than that one respondent, the rest of participants mentioned no other issues other than topics summarised above.

In particular no one mentioned any change in their opinion about withdrawal from treatment. There was also no mention about treatment whilst pregnant.

A9. Overall Opinion

Most of the respondents reported that they were, on balance, satisfied with the transition from eculizumab to ravulizumab and preferring to be on ravulizumab. Ravulizumab makes life easier. Some considered that both were necessary.

I definitely prefer ravulizumab…. ravulizumab I feel is a step above eculizumab **(**Patient C)

You have to have both eculizumab and ravulizumab available as options. It seems like some patients do better on one or the other. Some have had to go back to eculizumab. (Patient E)

Overall, she has done really well with the switch and she has not regretted it**.** (Carer Patient G)

My experience with ravulizumab has been phenomenal…I'm extremely happy with ravulizumab, and very grateful I get to have it (Patient H)

I can breathe, I feel better not having so much treatment, it's simpler to do, making life easier. (Patient L)

Switching to the 8-week ravulizumab has been an incredible blessing (Patient M)

SECTION B - Expected impact statements from patients who have experience of eculizumab only

B1. Transition process

Unlike patients from the USA, the UK patients were not anticipating the approval of a license by the European Medicines Agency. They did not seek it from their healthcare provider as soon as it was announced, being aware in any case that it would require further approval for all to benefit sometime in the future. They expected that once approval was given that careful coordination of the switch between eculizumab and ravulizumab would be needed to avoid mishaps.

I would hope that Newcastle will liaise with my consultant, who would liaise with homecare and the pharmacists, there does seem like a lot of potential for things to go wrong there! It would be helpful to get an information pack with details of the plans and reassurance of how the new drug works, perhaps an online question and answer session too (Patient B)

I realise there will be some transition stage from eculizumab to ravulizumab. I assume that Newcastle will contact my hospital who will then contact the homecare provider. I know that ravulizumab has a loading dose but after that I have no idea what the procedure is. (Patient C)

I would expect everyone involved, including the patient, to have a good working knowledge of ravulizumab and that the transition will be explained fully. From my memory of starting eculizumab the transition from plasma exchange was smooth – I would expect this to be the same (Patient D)

B2. Infusion Process

Participants were aware of the longer infusion time and the increase in the interval between infusions. UK patients placed more emphasis on fewer infusions bringing greater relief from the pressure, anxiety, and the damage from each infusion. Those receiving the infusion via a port catheter had concerns about what would be changed because of the longer gap.

…I also hate needles! Almost 7 years of infusions and it still isn't much better! The anxiety of a new nurse every 2 weeks who doesn't know you and can't access your veins isn't great so having to face this fear only every couple of months would be truly amazing! The more time goes on, the more visibly scarred my veins are becoming so being able to reduce that too (Patient A)

Different nurses every two weeks is another intrusion and their skills and knowledge vary greatly. The dread of having a nurse who you know struggles to cannulate you is awful and being calm whilst they stick you with a needle several times is very hard…***Week to week freedom, my infusion time is not guaranteed, so I can't make plans for Tuesdays every other week and when I was struggling with access two days either side. I have had to cancel plans made weeks in advance for one opportunity events but was made to feel that I had to fit into their very inflexible service. That did not feel good. It is hard to commit to others when planning something in the future which impacts on***

***friendships. It is very difficult to change the infusion time and if you have to you risk issues with delivery etc*.** (Patient B)

Reduced anxiety of treatment once every 8 weeks and not every fortnight…but will ports require heparin lock with the length of gap? (Patient C)

I find myself stressing about when the next infusion is, with that comes deliveries and timings that can be stressful too. I think I will feel a huge weight is lifted with 8 weeks breathing space….at present I cannot guarantee which day my infusion will be on every 2 weeks. I think I will just feel so much more 'normal' and enjoy the freedom to live life to the full. (Patient D)

B3. Efficacy of the Technologies

The UK patients' hope that ravulizumab would be as effective a treatment as eculizumab, which was the view of the US patients.

I just assumed and trusted that it would work as well and didn't consider the risks of coming off eculizumab the drug which keeps my much longed-for kidney transplant safe. I suppose I must trust the science and, as with eculizumab, I just believe it will work as well and keep me safe (Patient B)

I would like to think I would continue to be stable on ravulizumab as I am on eculizumab. (Patient D)

B4. Side Effects

Unlike US patients, the UK patients were more dismissive of the side effects of eculizumab/ravulizumab infusions though experiencing some transitory effects following each infusion. Particularly those who had long term experience of other more burdensome and damaging treatments. One patient considered whether ravulizumab impacted on the major side effect of complement inhibition i.e. meningococcal infection but expected current protection from the risk to work.

I know whatever the side effects are they will be better than side effects of dialysis!! People tell me there are side effects of eculizumab, but I don't experience any. I have my infusions and go! I have had heard the side effects maybe worse but perhaps, as I don't get any, I still won't. I think you can become hypervigilant to symptoms when you have a new drug, but I'll try to just truck on! (Patient B)

Risk of meningitis altered.... already on antibiotics so no other changes in meds needed. (Patient C)

I appreciate that newer patients struggle with side effects, but when you have survived purely on plasma exchange for 5 years as I did you don't complain about side effects because you know what life is like without these miracle drugs! (Patient D)

B5. Work, School and Other Activities

The UK patients expected, as the US patients have experienced, that the longer interval between infusions would have a significant impact on their working life, business opportunities and leisure. Some saw the opportunities for travel that they had put to one side while on eculizumab. Others who had travelled considered that the pressures of the uncertainties of being away from home would be lessened and would make such journeys more relaxing and "normal".

Working arrangements can be difficult when you work shift patterns in a hospital and need to constantly change your shift at short notice to accommodate your infusion, but not only that having to arrange the delivery and make sure someone is around to sign for it although you work all week can be awfully difficult; holidays are tricky to arrange as you have to assess your whole calendar and move your treatment dates sometimes which can take weeks due to the 48hr window (Patient A)

I have travelled and had my infusion away from home but that is very stressful and does impact on the holiday, the day before with the worry and the day of the infusion. Having an infusion on holiday means you miss out and is another reminder that you are not 'normal' like everyone else. Going away without having the infusion is also difficult because you are worrying about delays or problems getting home for your infusion. The Icelandic eruption would have been a disaster for my transplant and the recent pandemic too! (Patient B)

…can finally go on long-haul holidays and not limit to 12 nights in case of cancelled flights (Patient C)

I was diagnosed at 19 and it has always been my dream since that I would be able to travel. Eculizumab allowed me to travel for 2 weeks, but I always felt nervous that something might happen to prevent me returning on time for my infusion. With an 8-week regime I could satisfy my travel bug and feel confident I would have time if any travel plans are affected. (Patient D)

I run my own consultancy business, working for global organisations fixing commercial issues on a short- term project basis. Quite often, last minute projects or requests have come in that required me to travel with little notice. With the two-week schedule of eculizumab, I have been unable to take these jobs and lost out on lucrative jobs. (Patient E)

B6. General Health

UK patients did not expect any health improvement resulting from a switch to ravulizumab, other than a rumoured reduction in hypertension. The main health benefit foreseen would be in their mental health with the reduction in stress and anxiety about treatment.

The same as eculizumab it will improve my quality of life and my longevity. I would like to think the less regular infusion will reduce the stress and anxiety

over infusions and allow me to feel more confident and capable. I will continue to be active without the interruption of infusions! (Patient B)

I can guarantee you that my mental health and relationships will improve at least 10- fold. (Patient C)

I imagine one of the biggest impacts of Ravulizumab will be on my mental health. I can't emphasise enough the feeling of freedom this will give. I am a determined person anyway, but having this much time in between infusions will mean I can go for gold without any excuses of infusion dates etc. I don't always realise the impact of what having a long term, life changing illness can have on my mental health. It is only when I stop and look at it that I can see how trapped within aHUS that I can still feel even though I presently have 2 weeks between infusions (Patient D)

I would very much like to put more time between treatments as I feel this would improve my mental health (Patient E)

B7. Other Issues

Two respondents acknowledged the potential benefits to family/carers living with someone on ravulizumab treatment. Firstly, there would be less stress on and worry by carers about their support for home infusions etc, and greater career opportunities for spouses.

My family won't have to remember to stay in for the delivery of the drug every two weeks and the stress of whether it will arrive every two weeks. It won't have to be factored into planning our lives. Less stress with less frequent infusions and nurses who are strangers coming into the home. Feeling 'normal' like everyone most of the time. Less worry on holidays… Less worry for family wondering if infusions went ok. (Patient B)

My wife has twice been offered significant career opportunities that would require us living in the USA for a large part of the year. She felt compelled to turn them down due to my treatment schedule and proximity to care team. We've agreed that we wouldn't feel comfortable moving my healthcare away from the team at my hospital as we had bad experiences leading up to diagnosis getting the care I needed. However, if I was on ravulizumab it is feasible that I could manage my treatments, clinic appointment & travels to allow my wife to take these opportunities without feeling we're risking my health & care. (Patient E)

B8. Overall Opinion

UK patients felt the same as those from the USA about being able to access ravulizumab as a new treatment, that it would be preferred and add to the quality of their lives.

Being able to transfer my treatment to Ravulizumab would mean that my quality of life would be greatly improved…it may not sound like a big deal, but when you're lived through your 20s with that bind when seemingly everyone around

you has not a worry, it can be upsetting. To be able to get the last couple years of my 20s with such an 'easy' treatment option... amazing!! (Patient A)

Excited and probably when it comes to it nervous! (Patient B)

When we were allowed eculizumab I thought that was a life changer. But to have it every 8 weeks would be a miracle. I honestly can't wait for this change. (Patient C)

For the last 15 years I have required medical intervention at least every 2 weeks to keep me alive – the idea of having 8 weeks between medical treatments is amazing! When I was first diagnosed in 2005 the outlook was bleak, I can't quite believe there could be an opportunity to have a life that resembles 'normal'. I am stable on eculizumab and have been for over 10 years, whilst the idea of ravulizumab is very exciting I must admit there is a feeling of apprehension that it could be too good to be true. (Patient D)

My expectations for moving to ravulizumab are great and varied, as I am truly excited by the freedom the change in treatment schedule would make to my life. (Patient E)

4. Conclusion

From those USA patients with experience of both technologies, as well as the expectations of those in the UK on eculizumab now, the most telling benefit of ravulizumab over eculizumab is the substantial reduction in infusions needed, which increases the time between infusions considerably.

The fewer treatments reduces the cumulative pressure, anxieties, and practicalities of each treatment over time, as well as releasing additional personal time to do other things, including those put off because of the insufficient inter-treatment gap e.g. long-distance travel for leisure or education.

Of lesser importance to US participants, and even less so to UK patients, were the side effects of the new treatment. Most found little difference in post infusion transitory side effects, whether they had experienced any or none on eculizumab. Some perceived an improvement and two felt side effects had been sufficiently worse to revert, or think about reverting, to eculizumab. Those who had experienced and were aware of the long-term side effects of plasma exchange and dialysis therapies did not regard the transitory side effects of an infusion as burdensome.

With one exception, following transition participants had not observed any deterioration in the general health they attained whilst on eculizumab treatment. This was usually claimed to be excellent. UK patients saw mental health improvements as more likely.

With only minor logistical hiccoughs reported, the transition from one drug to another in the USA was not perceived as difficult to do, and so was not a matter of importance. Similarly, UK patients saw the potential for things going wrong, but which could be manageable by all parties involved in delivery.

Taken all together, patients with experience, and those with expectations, regard ravulizumab as adding to their quality of life. Although it was not within the scope of this research to measure and quantify a value of the quality of life added, based on what has been voiced by participants it can be confidently predicted that it would be more than zero.

From the evidence provided by those with experience of both eculizumab and ravulizumab treatments, as well as those with eculizumab experience only, patients see ravulizumab as a positive and progressive step change to their treatment. Although not perfect yet, it has much to commend it and is welcomed by aHUS patients.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the largest charity in the UK funding research into all aspects of kidney disease. The majority of our fundraising comes from our public supporters through donations, sponsored events, local fundraising activity, employee fundraising and other event fundraising. Other sources include partnerships with grant making trusts and charitable foundations, corporate partners (including industry) and other non-profit organisations. Finally, approximately a third of all our income comes from legacies and Gifts in Wills. We are registered with the Fundraising Regulator and a member of the Association of Medical Research Charities. Kidney Research UK is not a membership organisation.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Alexion: • £16,847 contribution towards a Fellowship Award – April 2020 • £7,200 support towards Fellows Day 2020 – Dec 2019. This grant is currently being held as a restricted grant for Fellows Day 2021.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient survey
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A selection of patient comments from our survey include: • my previous job was working abroad teaching, and that isn't possible really with fortnightly infusions. Were the situation different I might be able to return to Spain and my former employ with returning home for my infusion less of an issue. • Just before and after my infusion I feel exhausted and tired and am limited in what I can do. • I often miss events at school due to the infusion falling at the same time. • I mind applying for exciting jobs but having to tell them I'll need a half day each fortnight to go for my infusion. I mind losing that half days pay every single fortnight. I mind being put off applying for jobs because of knowing that my infusion will put them off me - whether that's legal or not. I mind never

	having been on a two week holiday because I'm scared something will go wrong and I'll be late for my eculuzimab. I mind the stress of trying to arrange even a weekend away because I have to figure out which Friday it will fall on. I mind that I had to choose to have it on a Friday afternoon because otherwise the times when that day or the following day are a write off would further impact my job. • Working arrangements can be difficult when you work shift patterns in a hospital and need to constantly change your shift at short notice to accommodate your infusion, but not only that having to arrange the delivery and make sure someone is around to sign for it although you work all week can be awfully difficult; holidays are tricky to arrange as you have to assess your whole calendar and move your treatment dates sometimes which can take weeks due to the 48hr window; social activities you may need to forget about because they are organised for the day of your infusion or you can't join a club that meets on that day because you'll only be able to go every 2 weeks. • Since I first became ill with ahus 15 years ago I have had many issues with my health and have spent a lot of time in hospital. After my second transplant 6 years ago I have felt very well and my life has become more normal again. Aside from the daily medication, the main thing that stops me feeling like I'm back to my old self is having the fortnightly infusions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	• my veins (which aren't amazing) are often battered and as happened this week, get blown and I have to wait a few days until another nurse can have a go. • I also hate needles! Almost 7 years of infusions and it still isn't much better! The anxiety of a new nurse every 2 weeks who doesn't know you and can't access your veins isn't great so having to face this fear only every couple of months would be truly amazing! The more time goes on, the more visibly scarred my veins are becoming so being able to reduce that too - amazing!! • I personally find the fortnightly infusion restrictive. Every fortnight having to leave the day free to receive the infusion.

8. Is there an unmet need for patients with this condition?	There is currently a safe and effective licensed treatment available to this patient group.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	• With a longer time elapse between infusion I think my veins would be less sore. • only having treatment every 8 weeks... it would be incredible, it would change my life so much! I'd like to say I live my life to the full and being able to do whatever I want pretty much whenever would be such a blessing! • Moving from 25 infusions to just 7 a year would make a massive impact on my life and almost make things feel normal • it causes less distress especially for younger Paediatric patients, being cannulated every 8 weeks versus 2 weeks is far less traumatic, it allows the veins to heal and enables a better quality of life. As a parent this provides us as a family with a significant change that is positive, attending every two weeks feels like you are never away from hospital and mentally it is exhausting for all with 2 weekly trips. Ravulizumab enables longevity in providing our son with less intervention, less interruption to daily life, fewer hospital trips and generally more time spent on the usual activities in life. The mental wellbeing for our family unit is significantly being increased with a 8 week treatment and makes it less traumatic for us all therefore improves our quality of life. • Having access to Ravulizumab , being administered only every 8 weeks would completely transform my life in that we would be able to fulfill dreams with my partner which until now seemed out of reach, like travelling further afield for longer periods of time. • I feel that being able to have my infusions every 8 weeks as opposed to 2 would really make a difference to my life. • I am currently re-reading a favourite book of mine "The Fellowship of the Ring" by J.R.R Tolkien and there is a part where Gandalf is speaking with Froddo and he says "all we have to decide is what to do with the time that is given us". This time is what Ravulizumab will give to myself and all aHUS patients

	who receive it. Something that you cannot get back and something that is truly priceless is time. We will be able to reclaim all the future time that would have been spent receiving an eculizumab infusion every 2 weeks. This time could be spent on a hobby, learning a new skill, spending time with loved ones or simply catching up on the latest 'must see' TV show. For me, this is 'extra' time. Time I had not accounted for or even expected I would have. More than the unrestricted holiday length, more than the reduction in the number of needles it is this additional time which is the true gift of Ravulizumab.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None reported in our survey
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Yes. There is a cohort of patients who would particularly benefit from this treatment - those who are unable to withdraw from eculizumab once in remission. Reasons for this would include people who have previously relapsed after withdrawal, those who have previously lost a transplant due to aHUS and those who have a high risk mutation in one of the complement genes.

please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Ravalizumab will significantly reduce hospital visits • Reduce number of cannulations for each patient • Reduce restrictions around work and travel • Significant improvement in quality of life as reflected in all patient comments •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association for Paediatric Nephrology**
3. Job title or position	**Consultant Paediatric Nephrologist**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAPN is an inclusive organisation open to all professionals working towards improving the care and lives of children with kidney diseases. It is a subsidiary of the Renal Association and is a charity funded by subscriptions
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	The BAPN trainee account received a total of £1666.67 from Alexion in November 2019 to support educational study days for junior doctors in training to become paediatric nephrologists

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent relapses of aHUS and to enable less frequent dosing for patients who need long term infusions
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	No relapse of aHUS whilst on treatment
8. In your view, is there an unmet need for patients and	There is currently an effective treatment (eculizumab) which is given every 2 to 3 weeks depending upon the weight of the patient. There is a desire to reduce the frequency of treatment in some patients

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With eculizumab
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	See next answer
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined in England. All suspected cases of aHUS are referred to the National Renal Complement Therapeutics Centre (NRCTC, where I am a member of the clinical team). Access to eculizumab follows clinical case discussion and elimination of differential diagnoses. Treatment is delivered by local clinical teams according to a shared care protocol between the local team and the NRCTC. The need for ongoing treatment is reviewed after results of all investigations (including genetic testing) and response to eculizumab treatment (at around 3 months). The process is different in devolved nations, but follows a broadly similar pattern and often includes advice from the NRCTC.

• What impact would the technology have on the current pathway of care?	I think that the initial care pathway would remain the same. However once a need for ongoing treatment has been established (at around 3 months) then an option to switch to ravulizumab could be introduced.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As above – would be substituted for eculizumab once need for ongoing treatment is established.
• How does healthcare resource use differ between the technology and current care?	This would result in reduced frequency of health care visits (from every 2 weeks currently to every 4 weeks if under 20kg and every 8 weeks if over 20kg). It should be noted that many of these encounters are currently provided by private home care providers, funded by the manufacturer of eculizumab
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary adult care and tertiary paediatric care, under the guidance of the national centre (in England), often outsourced to private home care providers as above
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	In England the NRCTC will need to review all patients currently receiving eculizumab and determine who could switch to ravulizumab. Specialist nurse counselling for patients will be advised to help patients decide whether to switch. In devolved nations a similar process will be needed.
11. Do you expect the technology to provide clinically	I think the clinical outcomes will be broadly similar. The outcomes to consider would be quality of life, time off work and education and health care professional time

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I understand that it would not be appropriate for use in pregnant women due to the mechanism of action. Eculizumab is currently used in pregnant women
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	It will be equally easy to use as eculizumab As above – less frequent administration visits will be required

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Since we anticipate using only in those in whom a need for ongoing treatment is established, there is unlikely to be a need for start or stop treatment at present. However once the results of the eculizumab withdrawal trial (SETS-aHUS) are available, there are likely to be protocols for stopping and starting ravulizumab to use it only during relapses. This will not differ from existing care (ie this will happen anyway with eculizumab, not just with ravulizumab)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	It will give patients more freedom to travel and potentially to retain employment. It will be extremely important to hear patients' perspective on this

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is a risk of meningococcal disease, as with eculizumab. This requires patients to be vigilant for signs and symptoms and to present to health care when unwell. There would be no difference to their current QoL on eculizumab treatment in this regard
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Generally yes. I think that the trials included a broader spectrum of patients than are currently treated with eculizumab in the UK
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Haematological remission (normalisation of platelets), renal remission (estimated GFR and use of renal replacement therapy) and death These were all measured in the only published trial so far, studying ravulizumab in adults with presumed aHUS (Rondeau et al Kidney international 2020). Importantly the proportion of patients who came off renal replacement therapy (i.e. significant improvement in kidney function) was different between the eculizumab trial (Fakhouri Am J Kid Dis 2016) and this trial (83% of those in the eculizumab trial came off and 58.6% of those in the ravulizumab trial came off). Also there were 4 deaths in the ravulizumab trial and no deaths in

	the eculizumab trial. These were not thought to be treatment related by the investigators. The authors acknowledge that the reduced rate of coming off renal replacement therapy and the increased deaths may be due to a broader inclusion of patients in the ravulizumab trial, which may have included some patients whose clinical picture was not ultimately due to aHUS. This is supported by the reduced rate of complement abnormalities in patients in the ravulizumab trial (20.5%) compared with previous studies in aHUS patients (60-70%). Paediatric data from the ALXN1210-312 trial are imminently awaited. In the eculizumab trials, the effect seen in adults was replicated in children.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	I am not aware of any real-world use of ravulizumab in aHUS yet In the UK I think we would apply stricter criteria for starting ravulizumab than were applied in the clinical trial, in order to exclude more patients whose ultimate diagnosis is not aHUS
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	n/a
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- An effective treatment for aHUS is already available therefore this is an incremental change
- Capturing patient opinion about the impact of ravulizumab on their quality of life is important
- QoL data for children should include disruption to education and socioeconomic impact on the family
- Modelling the impact on healthcare provider time is important
- The paediatric trial has not yet reported

Thank you for your time.

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Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation UK Renal Pharmacy Group

Please indicate your position in the organisation:

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

N/A

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

What is the expected place of the technology in current practice?

Treatment of aHUS is well controlled and centrally regulated via Newcastle aHUS centre. Treatment with eculizumab cannot be initiated or funded without their approval. However as ravulizumab has a half-life four times that of eculizumab (comparator) this will have a significant impact on patient's life's as they will only have to have a maintenance infusion every 8 weeks rather than every 2 weeks as is current best treatment with eculizumab. As well as a positive impact on patient's quality of life there will also be a considerable cost benefit to NHS from the reduced infusion frequency – staff time, consumables, monitoring, blood tests, travelling times to administer infusions. Many of these patients receive their infusions at home via homecare services and there are significant costs associated with this. Per annum – 26 eculizumab infusions versus 6 for ravulizumab. This reduced infusion frequency is a considerable advantage to current standard of care with eculizumab.

I am not aware of geographical variation in practice due to central monitoring control of Newcastle aHUS centre.

Potential impact on the NHS if NICE recommends the technology

Potential impact would be significant cost efficiencies to NHS and health economy. In trials the safety and tolerability of ravulizumab and eculizumab were comparable and the two drugs have a similar safety profile. So to offer a replacement drug that could be administered every 8 weeks rather than every 2 weeks will have a positive impact for patients and the wider health economy.

Ravulizumab can only be initiated and prescribed in secondary care via specialist clinics. On-going maintenance doses can be administered in primary care setting at patients home via homecare services. Ravulizumab will allow extension of dosage interval to 8 weekly from current 2 weekly dosing with eculizumab which will impact positively on patients.

The reduced frequency of dosing will result in cost savings from drug and administration costs including homecare services.

The same training requirements are necessary for ravulizumab as for eculizumab.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Would there be any need for education and training of NHS staff?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

……

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS ENGLAND
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for atypical haemolytic uraemic syndrome **(**aHUS).

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a highly specialised service (HSS) for the treatment for the treatment of aHUS commissioned through a single centre. The HSS coordinates the use of the currently available treatment eculizumab through a national protocol, undertakes national surveillance, participates in research and provides expert opinion on treatment and diagnostics to other centres. Patients remain under the care of local clinicians using shared care protocols which specify the requirements of both parties in the ongoing management of cases.
8. What impact would the technology have on the current pathway of care?	The technology will not alter the current pathway of care
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This drug is not commissioned for routine use by NHS England.
10. Will the technology be used (or is it already used) in	It is anticipated the technology would be administered through the HSS under existing arrangements

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for this patient cohort.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Within the HSS using shared care protocols
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	

11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues.
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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Evidence Review Group's Report

Ravulizumab for atypical Haemolytic Uremic Syndrome

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None

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Sheerin, Professor of Nephrology, Institute of Cellular Medicine, Newcastle University, for their clinical advice throughout this project. David Kavanagh and Neil Sheerin also acted as clinical advisers to the company for this submission; Neil Sheerin advised the company on the indirect treatment comparison analyses.

Rider on responsibility for report

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

This report should be referenced as follows:

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Contributions of authors

Georgios Nikolaidis critiqued and performed the economic analyses and wrote Sections 4, 5 and 6 of the report.

Alexis Llewellyn critiqued the clinical effectiveness review and wrote Section 3 of the report.

Laetitia Schmitt performed the economic analyses and contributed to Sections 4, 5 and 6 of the report.

Nick Meader critiqued the clinical effectiveness review and wrote Sections 2 and 3 of the report.

Simon Walker provided expert advice on the economic analyses and the report as a whole.

Melissa Harden critiqued the company search strategies and provided information support.

Claire Rothery critiqued the economic analyses, contributed to Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Alison Eastwood provided advice, commented on drafts of the report, led the overall clinical effectiveness sections and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been redacted, all academic-in-confidence (AIC) data are redacted, all depersonalised data (DPD) redacted.

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List of abbreviations

AE	Adverse event
aHUS	Atypical haemolytic uraemic syndrome
CI	Confidence interval
CKD	Chronic kidney damage
CS	Company submission
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
ESRD	End stage renal disease
FAS	Full analysis set
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
HUS	Haemolytic uraemic syndrome
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LOCF	Last observation carried forward
LYG	Life year gained
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLS	Ordinary least squares
ONS	Office for National Statistics
PE/PI	Plasma exchange/infusion
PICO	Population, intervention, comparators, outcomes

PNH	Paroxysmal nocturnal haemoglobinuria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TMA	Thrombotic microangiopathy
TTO	Time trade-off
TTP	Thrombotic thrombocytopenic purpura

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID1530	Summary of issue	Report sections
1.	Generalisability of the ravulizumab trials to NHS practice Most of the ravulizumab trial population is not representative of patients who would be eligible in UK clinical practice. Most trial evidence includes eculizumab naïve patients; however, it is expected that nearly all eligible patients in clinical practice would initially receive eculizumab treatment for at least 3 months and only after a response has been demonstrated (or correct diagnosis determined) these patients would switch to ravulizumab treatment.	3.2.1 and 3.2.2
2.	Relative efficacy of ravulizumab versus eculizumab Despite the substantial biological similarity between ravulizumab and eculizumab, there is insufficient evidence to support the assumption that these treatments have equivalent efficacy and safety. All aHUS evidence for ravulizumab and eculizumab is based on single-arm trials. Clinically relevant differences between the ravulizumab and eculizumab trial populations, limitations of the indirect treatment comparison between the two treatments, and significant study quality concerns mean that indirect comparisons between the two treatments are highly uncertain and at high risk of bias. The data are too limited to predict the direction and magnitude of this bias. Equivalence in efficacy and safety between the two treatments is a key assumption of the company's economic model.	3.4, 4.2.7 (item 8), and 6.1.2.1
3.	Long-term efficacy and safety of ravulizumab There is insufficient follow-up data to conclude on the long-term safety and efficacy of ravulizumab. In the company model, long-term efficacy and safety of ravulizumab are assumed to be equivalent. Although this is clinically plausible, there is no evidence to support this assumption.	3.2.3 and 3.2.4
4.	Relapse rate following treatment discontinuation The company assumes that patients who discontinue treatment experience a risk of relapse that is constant through time. However, evidence from the literature suggests that the risk of relapse is higher shortly after treatment withdrawal and is substantially reduced after around one year of sustained disease control. This issue has important implications for the proportion of patients in the model who are back on -lifelong- treatment in the long-term.	Section 4.2.3 (item 3)

Table 1 continued.		
5.	Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations. The company assumes that patients who discontinue treatment and their disease subsequently relapses will re-initiate treatment and receive it for the remainder of their lifetime (and are not permitted to discontinue treatment again). It is likely that clinical practice will soon switch from lifelong treatment to treating aHUS patients `on-demand'. As a result, patients who re-initiate may only be on treatment during a proportion of their lifetime.	Section 4.2.3 (item 4)
6.	Treatment discontinuation due to renal response Although current guidelines suggest that treatment should be given lifelong, there are several arguments presented in the literature opposing this view when adequate renal response has been achieved, and several trials have attempted to discontinue treatment in patients who respond to complement-inhibitor treatment. The ERG expects that once the SETS study reports, current practice is likely to change, and lifelong complement-inhibitor treatment will not be standard in patients who show adequate renal response.	Section 4.2.3 (item 1)
7.	The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future. Despite that eculizumab (Soliris) is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years[1] and biosimilar eculizumab treatments are likely to enter the market.	Section 4.2.5

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are: (i) the inclusion of renal response as a reason for treatment discontinuation, (ii) the use of time-dependent relapse rates, and (iii) addressing the potential for using complement-inhibitor treatment only `on demand'.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is not modelled to affect QALYs as the company's base case comprises a cost-minimisation analysis.

Overall, the technology is modelled to affect costs by:

[redacted]

The modelling assumption that has the greatest effect on the ICER is:

- The proportion of a patient's lifetime over which they would receive treatment after the first disease relapse.

1.3 The decision problem: summary of the ERG's key issues

The population defined in the NICE scope includes patients who have had eculizumab treatment for at least 3 months and whose disease has responded to eculizumab, as well as eculizumab treatment-naïve patients. It is expected that nearly all patients who would be eligible for ravulizumab in the NHS would have shown prior response to eculizumab. However, most of the evidence from the ravulizumab trials includes eculizumab treatment-naïve patients and the economic analysis explicitly considers treatment-naïve patients due to the lack of evidence on patients who have switched from eculizumab. This is further discussed in Section 1.4.

Eculizumab is the only comparator in the company's analyses. Although eculizumab is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years and biosimilar treatments may enter the market. This is further discussed in Section 1.6.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 1 Generalisability of the ravulizumab trials to NHS practice

Report section	3.2.1 and 3.2.2
Description of issue and why the ERG has identified it as important	The ravulizumab trial population is not representative of the NHS aHUS population who would be eligible for ravulizumab therapy. All of the trial evidence in adults and most of the paediatric evidence for ravulizumab is based on eculizumab-naïve patients. However, it is expected that nearly all eligible patients in NHS practice would receive ravulizumab treatment only after they have received eculizumab for at least 3 months and who have shown response to eculizumab. There are significant differences in baseline characteristics between treatment naïve patients and eculizumab-experienced patients switching to ravulizumab. In addition, a significant proportion of patients in the ravulizumab trials may not have aHUS. This significantly limits the generalisability of the trial evidence to the NHS.
What alternative approach has the ERG suggested?	There is insufficient evidence to inform outcomes in patients who have switched from eculizumab to ravulizumab.
What is the expected effect on the cost-effectiveness estimates?	Total costs for ravulizumab would be expected to increase because of the increased number of infusions associated with receiving prior eculizumab treatment, while the impact on QALYs is unknown due to the lack of evidence on outcomes for patients who have switched from eculizumab.
What additional evidence or analyses might help to resolve this key issue?	Additional ravulizumab evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS.

Issue 2 Relative efficacy of ravulizumab versus eculizumab

Report section	3.4, 4.2.7 (item 8), 6.1.2.1
Description of issue and why the ERG has identified it as important	Despite the substantial biological similarity between ravulizumab and eculizumab, there is insufficient evidence to support the assumption that these treatments have equivalent efficacy and safety. All aHUS evidence for ravulizumab and eculizumab is based on single-arm trials. Therefore, the company conducted prognostic score matching using stabilized weights to reduce baseline differences observed between the eculizumab and ravulizumab trial populations. Indirect treatment comparison (ITC) analyses did not match for the presence of pathogenic variants, despite substantial differences between treatments, and results showed that differences in effectiveness between treatments cannot be ruled out. The absence of RCT evidence, clinically relevant differences between the ravulizumab and eculizumab trial populations, limitations of the ITC and significant study quality concerns mean that indirect comparisons between the two treatments are highly uncertain and at high risk of bias. The data are too limited to predict the direction and magnitude of this bias. Equivalence in efficacy and safety between the two treatments is a key assumption of the company's economic model.
What alternative approach has the ERG suggested?	The ERG conducted an analysis assuming differential efficacy based on the company's ITC analysis. Further details are provided in Section 6.1.2.1.
What is the expected effect on the cost-effectiveness estimates?	Assuming differential efficacy reduced the cost-effectiveness of ravulizumab because the ITC analysis implies that ravulizumab is less effective than eculizumab. The impact is minimal though, and ravulizumab remains cost-effective. However, the ERG highlights that the insensitivity of the conclusions is reliant on key assumptions employed in the economic model. Specifically, if more information was available regarding the relapse rates, the possibility of providing treatment `on demand', and the potential availability of biosimilar treatments, the impact of differential efficacy on cost-effectiveness could be substantial.
What additional evidence or analyses might help to resolve this key issue?	Randomised evidence of ravulizumab versus eculizumab in aHUS patients would help clarify whether the assumption of equal efficacy and effectiveness is justified. However, the ERG acknowledges that given the ultra-rare nature of the disease, this evidence may never become available. Where possible, establishing non-inferiority between the treatments in a trial programme for aHUS may be required.

Issue 3 Long-term safety and efficacy of ravulizumab

Report section	3.2.3 (efficacy), 3.2.4 (safety)
Description of issue and why the ERG has identified it as important	There is no follow-up data to inform the long-term safety and efficacy of ravulizumab. In the company model, long-term efficacy and safety of ravulizumab are assumed to be equivalent. Although this is clinically plausible, there is no evidence to support this assumption.
What alternative approach has the ERG suggested?	Alternative assumptions on discontinuation, relapse rates and alternative long-term treatment strategies are explored (see section 1.5, Issue 4 to Issue 6.
What is the expected effect on the cost-effectiveness estimates?	See section 1.5, Issue 4 to Issue 6.
What additional evidence or analyses might help to resolve this key issue?	Longer-term efficacy and safety follow-up data of patients currently enrolled in trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312, and long-term efficacy (including recurrence and quality of life) and safety data for eculizumab experienced patients who switched to ravulizumab. As with eculizumab, long-term studies on treatment withdrawal and alternative treatment strategies for ravulizumab are required. The duration of the ongoing trial extension period may be dependent on approval of ravulizumab in the NHS and other healthcare systems and may therefore not be sufficient to resolve this issue.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 4 Relapse rate following treatment discontinuation

Report section	4.2.3 (item 3)
Description of issue and why the ERG has identified it as important	The company assumes that patients who discontinue treatment experience a risk of relapse that is constant through time. However, evidence from the literature suggests that the risk of relapse is higher shortly after treatment withdrawal and is substantially reduced after around one year of sustained disease control. This issue has important implications for the proportion of patients in the model who are back on lifelong treatment in the long-term.
What alternative approach has the ERG suggested?	The ERG considers time-dependent relapse rates to be a more appropriate approach. The ERG conducted time-to-event analysis to estimate the risk of relapse over time using evidence from UK patients enrolled in the global aHUS registry. This is described in detail in Section 6.1.1.2
What is the expected effect on the cost-effectiveness estimates?	Implementing time-dependent relapse rates in the model increased the incremental costs and potential cost-savings associated with ravulizumab compared with eculizumab. This was because the estimated relapse rates were higher than the company's constant relapse rate for the first 7.6 years in adults and 6.6 years in children, and lower only thereafter. The model also assumes that once patients' relapse, they are re-initiated on lifelong treatment. The ERG highlights that the time-to-event analysis is based on a small number of UK patients and therefore the derived relapse rates over time are surrounded by considerable uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Conducting time-to-event analysis using the full cohort of patients enrolled in the aHUS registry who discontinued treatment could significantly reduce uncertainty and help inform the economic model with more appropriate time-dependent relapse rates.

Issue 5 Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations

Report section	4.2.3 (item 4)
Description of issue and why the ERG has identified it as important	The company assumes that patients who discontinue treatment and their disease subsequently relapses will re-initiate treatment and receive it for the remainder of their lifetime (and are not permitted to discontinue treatment again). The ERG considers it likely that clinical practice will soon switch from lifelong treatment to treating aHUS patients `on-demand'. As a result, patients who re-initiate may only be on treatment during a proportion of their lifetime.
What alternative approach has the ERG suggested?	The ERG acknowledges that there is a paucity of evidence surrounding second and subsequent treatment discontinuations and highlights that this as an area of considerable uncertainty with high potential impact on incremental costs and cost-effectiveness. To reflect the plausibility of providing treatment `on-demand', the ERG assumed that patients who relapse and re-initiate treatment would receive treatment only for a proportion of their remaining lifetime. The ERG presents cost-effectiveness estimates for a wide range of possibilities from 50% - 100%. In the former, patients who relapse receive treatment only for 50% of their remaining lifetime, whilst in the latter they receive treatment for 100% (i.e. lifelong treatment as assumed in the company's base case). More details are provided in Section 6.1.1.3.
What is the expected effect on the cost-effectiveness estimates?	Accounting for the potential of multiple discontinuations by reducing the proportion of a patient's lifetime that they are on treatment after disease relapse implies a substantial reduction in the total incremental costs and potential cost-savings of ravulizumab compared with eculizumab. However, ravulizumab remains a cost-saving treatment option compared with eculizumab based on the modelled assumptions and evidence available.
What additional evidence or analyses might help to resolve this key issue?	Once the SETS study[2] reports, a similar study could be designed that would seek to evaluate whether patients who relapse following disease relapse and treatment re-initiation can safely be withdrawn from treatment for a second or further time.

Issue 6 Treatment discontinuation due to renal response

Report section	4.2.3. (item 1)
Description of issue and why the ERG has identified it as important	The company's base-case did not consider treatment discontinuation due to adequate renal response. Although current guidelines suggest that treatment should be given lifelong, there are several arguments presented in the literature opposing this view when adequate renal response has been achieved, and several trials have attempted to discontinue treatment in patients who respond to complement-inhibitor treatment. The ERG expects that once the SETS study reports, current practice is likely to change, and lifelong complement-inhibitor treatment will not be standard in patients who show adequate renal response.
What alternative approach has the ERG suggested?	The ERG suggests that discontinuation due to adequate renal response is considered as a reason for treatment discontinuation
What is the expected effect on the cost-effectiveness estimates?	The total incremental costs of ravulizumab compared with eculizumab are reduced by [redacted] in the ERG's base case analysis, which is relatively small compared to the impact of the other assumptions in the model.
What additional evidence or analyses might help to resolve this key issue?	None required.

1.6 Other key issues: summary of ERG's view

Issue 7 The submission does not consider eculizumab biosimilars

Report section	4.2.5.
Description of issue and why the ERG has identified it as important	The company compares ravulizumab (Ultomiris) with eculizumab (Soliris). Although eculizumab (Soliris) is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years[1] and biosimilar eculizumab treatments are likely to enter the market.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The introduction of eculizumab biosimilars could reduce the costs of eculizumab and therefore could also reduce the cost-effectiveness of ravulizumab. Depending on the actual discount that a biosimilar would offer compared to eculizumab, ravulizumab may or may not still be the cost-effective option.
What additional evidence or analyses might help to resolve this key issue?	1. A detailed list of the eculizumab biosimilar treatments that are currently under development, their expected time of entering the market, and their expected prices. 2. An assessment of whether it can be realistically expected that a switch in practice from eculizumab to ravulizumab would not discourage a proportion of patients switching back to eculizumab.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Table 2 Summary of the ERG's preferred assumptions and ICERs

	Incremental costs (£)	Incremental QALYs	ICER for RAV vs ECU
Company's base-case	[redacted]	[redacted]	[redacted]
1. Include renal response as a reason for treatment discontinuation	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Assume time-dependent relapse rates following treatment discontinuation	[redacted]	[redacted]	[redacted]
3. Analysis 2 + Account for the potential of multiple treatment discontinuations (The presented ranges correspond to treatment re-initiation for a proportion of 50% and 100% of a patient's remaining lifetime) **ERG's PREFERRED BASE-CASE**	[redacted]	[redacted]	[redacted]
ERG's base case + assuming differential efficacy*	[redacted]	[redacted]	[redacted]

*This scenario corresponds to Scenario 1b in Table 22, which does not include the additional QALY increment for RAV based on the company's discrete choice experiment.
ǂ ICER in the South-West quadrant of the Incremental cost-effectiveness plane with higher values indicating that RAV is more likely to be cost-effective compared to eculizumab. RAV: ravulizumab; ECU: eculizumab

For further details of the exploratory and sensitivity analyses conducted by the ERG, see Section 6.1.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Background

2.1.1 Previous NICE appraisals on complement-inhibitor therapies for aHUS

NICE has previously appraised eculizumab, which is a complement-inhibitor treatment functioning through the same mechanism as ravulizumab, as a highly specialised service in HST1 for the treatment of aHUS. HST1 recommends the use of eculizumab for the treatment of both adult and paediatric patients with aHUS.[3]

2.1.2 Disease Background

The ERG agrees that the company's summary of atypical haemolytic uremic syndrome (aHUS) provides an appropriate and relevant background to the decision problem.

The underlying pathophysiology of aHUS is uncontrolled terminal complement activation in the alternative pathway (AP) of complement. Complement regulatory gene/protein mutations or autoantibodies are detected in approximately 50-70% of patients.[4] In the UK, genetic or acquired complement abnormalities were identified in 69% of patients with aHUS.[5]

Since there is no specific test, aHUS is a clinical diagnosis of complement-mediated thrombotic microangiopathy (TMA) and requires exclusion of thrombotic thrombocytopenic purpura (TTP) and STEC (Shiga toxin-related Escherichia coli) infection.

Critique

Although historically life-long treatment has been proposed for eculizumab, there is very limited evidence to support this practice.[6] In response to NICE recommendations, the Stopping Eculizumab Treatment Safely (SETS) trial[7] is currently investigating the impact of eculizumab withdrawal and is expected to be completed in 2022.

A recent review found nine case-reports studying the impact of withdrawing eculizumab in patients who had responded to treatment.[6] Overall, 27% of patients relapsed in these studies. The median time to relapse across studies was 3 months, suggesting that those who relapsed were more likely to do so soon after discontinuation.[6]

The CS stated (based on an advisory board meeting of clinical experts) that patients who relapsed were expected to remain on treatment indefinitely. However, minutes from one of the company advisory board meetings indicate greater uncertainty: "[redacted]".[8]

2.1.3 The technology and the company's anticipated positioning of ravulizumab

The ERG considers the company's description of the technology to be appropriate. Ravulizumab is a monocolonal antibody (mAB) treatment that acts as a complement inhibitor. Ravulizumab is a re-engineering of eculizumab to extend the half-life of the drug. Both ravulizumab and eculizumab bind to complement protein C5 inhibiting terminal complement-mediated inflammation and preventing immune activation and haemolysis. Although both treatments function through the same mechanism, ravulizumab binds to its substrate with higher affinity and achieves a quadruple half-life; thus, requiring less frequent administration. Therefore, adults require ravulizumab every 8 weeks compared with every 2 weeks for eculizumab (and 4 weeks vs 2 weeks for paediatric patients <20 kg).

The CS positioned ravulizumab as an alternative treatment option to eculizumab (with the exception of paediatric patients weighing less than 10kg). In response to question A2 of points for clarification (PFCs), the company expected ravulizumab to be offered as either:

- first-line treatment option for complement-inhibitor treatment naïve population, or
- second-line/maintenance treatment in people who had received eculizumab for at least three months and had evidence of response.

Points for critique

Clinical advice provided to the ERG, suggested that in nearly all cases, ravulizumab would be provided as a second-line/maintenance treatment for people who had responded to eculizumab. Because aHUS is a diagnosis of exclusion, the shorter half-life of eculizumab is beneficial at the initiation of treatment since there is a shorter duration time required to discontinue treatment when evidence of an alternative diagnosis becomes available. Although, clinical advisers pointed out in some paediatric patients, where it is challenging to maintain central lines for a long period of time, ravulizumab may potentially be a first-line treatment option. However, most of the evidence from the ravulizumab trials included eculizumab treatment-naïve patients and the economic analysis explicitly considered treatment-naïve patients due to the lack of evidence on patients who had switched from eculizumab.

A further factor impacting the positioning of ravulizumab, not mentioned in the CS, is the likely availability of several biosimilars (oral and subcutaneous treatments), potentially within the next five years. Therefore, the positioning of ravulizumab may change as these alternative treatments become available.

2.2 Critique of company's definition of decision problem

The company submission generally reflected the NICE decision problem, although the ERG has concerns about the trial population not being reflective of most patients who would receive ravulizumab in clinical practice, and the expected availability of biosimilar comparators in the relatively near future. A summary and critique of the company's definition of the decision problem is presented in Table 3.

Table 3 Summary and critique of decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**	**ERG comment**
Population	People who weigh 10kg or more with atypical haemolytic uremic syndrome (aHUS) and: • who have not had complement inhibitor treatment, or • who have had eculizumab for at least 3 months and whose disease has responded to eculizumab	People who weigh 10kg or more with atypical haemolytic uremic syndrome (aHUS) and: • who are complement inhibitor treatment-naive, or • have received eculizumab for at least 3 months and have evidence of response to eculizumab	Wording has been aligned to the market authorisation.	The evidence presented by the company largely reflected the NICE decision problem. However, the ERG identified some concerns: • Very limited evidence presented on aHUS patients who responded to eculizumab (data was only available for 10 paediatric patients). This is an important limitation, since ERG clinical advisers expected almost all patients in UK clinical practice would receive ravulizumab after responding to eculizumab. • According to clinical advisers to the ERG, the low prevalence of identified genetic variants in some of the ravulizumab trials suggested many of the patients did not have aHUS.
Intervention	Ravulizumab	Ravulizumab	Not applicable	The intervention described in the company's submission matches the intervention described in the final scope.
Comparator(s)	Eculizumab	Eculizumab	Not applicable	Comparators described in the company's submission matched the comparators described in the final scope. However, clinical advisers to the ERG pointed out that current practice for aHUS is likely to change substantially in the next 3-5 years. As discussed above, although eculizumab is currently the only available comparator, as eculizumab biosimilars become available this is likely to have a substantial impact on

				the positioning of ravulizumab in NHS practice in the relatively near future.
Outcomes	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clincal outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clincal outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment • Health-related quality of life	The company noted that some outcomes (overall survival, disease re-currence, and eligibility for/success of transplantation) included in the final scope were not pre-specified in the ravulizumab trial programme. Overall survival was modelled in the pharmacoeconomic analyses and death was captured as a safety outcome. Because follow up for ravulizumab trials were of insufficient duration, disease recurrence was not collected. However, TMA parameters were included in these trials. Disease recurrence in the CS was modelled in the pharmacoeconomic analyses using longer term data from eculizumab trials. Eligibility for/success of transplantation was not measured in trials. However, CKD stage was captured in trials and included in economic modelling.	The outcomes largely match the final scope. The company appropriately pointed out some outcomes were not available in the ravulizumab trials.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an	The economic analysis base case assumes equal efficacy and effectiveness between ravulizumab and eculizumab and only compares the differences in treatment costs. A scenario analysis considered differential effectiveness based solely upon CKD stage outcomes, and models the differences between QALYs and costs for ravulizumab and eculizumab. The cost-effectiveness of treatments in the scenario analysis is expressed in terms of cost per QALY. A lifetime time horizon is used and costs are considered from an NHS and Personal Social Services perspective.	Not applicable	The CS is in line with the final scope issued by NICE. The appropriateness of the cost-minimisation analysis for evaluating the cost-effectiveness of ravulizumab is dependent on the clinical equivalence of ravulizumab and eculizumab in terms of efficacy, safety, and health-related quality of life (and uncertainty surrounding these outcomes). Adult and child populations were modelled separately with the cost-effectiveness results weighted based on the proportion of adults versus children currently treated in clinical practice. This approach is considered appropriate given the evidence available.

	NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	N/A	N/A	N/A	N/A
Special considerations including issues related to equity or equality	N/A	N/A	N/A	N/A

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify the available clinical evidence for the current treatment options for patients with atypical haemolytic uremic syndrome (aHUS), including eculizumab and ravulizumab. The systematic review methods are reported in the CS Document B, Appendix D. This section provides a brief summary and critique of the systematic review methods.

Overall, the ERG found that the review methods for searching, extracting and quality assessing studies were broadly appropriate. However, the ERG believes the selection of studies was too restrictive and excluded relevant studies on the safety of ravulizumab and eculizumab.

3.1.1 Searches

Literature search methodology is reported in CS Document B, Appendix D.1.1. Searches included key databases (MEDLINE, EMBASE and Central Register of Controlled Trials) up to April 2020. An OVID search strategy was reported, and relevant conference proceedings were consulted. The search strategy was designed to pick up any interventions for aHUS. No reference checking was reported, and it does not appear that validated filters for study designs were used.

3.1.1.1 Points for critique

Despite some limitations, the ERG believes that the review search strategy was broadly appropriate and is unlikely to have missed relevant studies up to April 2020. Appendix A, Table 23 contains the ERG appraisal of the searches.

3.1.2 Study selection

The study selection process is reported in CS Document B, Appendix D.1.2. Eligibility criteria are presented in CS Document B, Appendix D, Table 2. Participants with a diagnosis of aHUS receiving ravulizumab, eculizumab, plasma therapy, kidney transplantation, liver-kidney transplantation, immunosuppression therapy or dialysis were included. Any efficacy and safety outcomes were included. Eligible study designs included randomised, non-randomised, single-arm, prospective and retrospective studies. Studies reported in a non-English language were excluded. A PRISMA flow diagram was reported in CS Document B, Appendix D, Figure 1. A total of 55 unique studies were included. A list of references with a brief description of the design and intervention is presented in CS Document B, Appendix D, Table 3. Two studies of ravulizumab were included (the single-arm trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312), and 37 non-comparative studies of eculizumab, of which four were single-arm trials (aHUS-C08-002, aHUS-C08-003, aHUS-C10-003, aHUS-C10-004).

Following initial study selection, a feasibility analysis was conducted to determine which trials identified in the systematic review were appropriate for inclusion in an indirect treatment comparison. Details of the selection process are presented in CS Document B, Appendix D, Section D.1.4. Only studies with individual patient datasets "available to Alexion" were considered for inclusion in the indirect treatment comparisons. The company did not state whether any attempts were made to retrieve individual patient datasets not already held by them. The feasibility analysis included 'cleaning' of individual patient level data, tabulation of patient characteristics and outcomes measures, qualitative comparison of data available and identification of key differences between studies and homogeneous subgroups. A number of additional exclusions resulted from the feasibility analysis, notably: clinically stable patients following eculizumab therapy (as all patients enrolled in eculizumab trials were complement inhibitor treatment-naïve); patients who were clinically stable following long-term plasma therapy (such as those included in trial aHUS-C08-003, as they are not represented in the ravulizumab trials); and the global aHUS registry of 1,794 participants due to data quality concerns (no formal monitoring of data collection, only six month intervals assessments) and risk of double counting (overlap with eculizumab trial population).

Of the 55 studies included in the systematic review, only five single-arm trials were included following the feasibility analysis: two ravulizumab trials (ALXN1210-aHUS-311 and ALXN1210-aHUS-312) and three eculizumab trials (aHUS-C08-002, aHUS-C10-003 and aHUS-C10-004). Patient characteristics and outcomes of studies included in the systematic review but subsequently excluded from the indirect treatment comparison were not presented.

3.1.2.1 Points for critique

Although the systematic review eligibility criteria were generally appropriate to identify relevant studies of aHUS participants, the feasibility analysis conducted by the company led to the exclusion of most aHUS studies (50 out of 55 identified), and to the inclusion of only a subset of ravulizumab and eculizumab single-arm trials with individual patient data (total N=139). In particular, all observational evidence on eculizumab, including data on long-term efficacy and safety from the aHUS global registry data of 1,794 participants was not presented in the CS.

As no comparative trials were found and selection of studies was restricted to aHUS patients, broadening the selection criteria to include head-to-head randomised comparisons of ravulizumab against eculizumab, such as trial 301[9] would have identified broader indirect evidence informing the relative safety profiles of these treatments. Language restrictions mean that the risk of missing relevant non-English language studies cannot be excluded.

3.1.3 Data extraction

The data extraction process is described in CS Document B, Appendix D, Section D.1.3.

The CS stated that double data extraction was performed for all data of interest from the eligible studies, and that summary tables and summary tables and a narrative description of the study designs used, data collected, and outcomes reported were assembled into a final report. Extracted data were only presented for the five studies included in the indirect treatment comparison.

3.1.3.1 Points for critique

The process for conducting data extraction was generally appropriate. Where available, appropriate disease characteristics and outcomes were extracted. However, extracted data were only presented for the five studies that were included in the indirect treatment comparison.

3.1.4 Quality assessment

Quality assessment of single-arm studies identified through the systematic review was conducted using the STROBE statement for observational studies,[10] and risk of bias was considered in an adapted version of the Cochrane Risk of Bias assessment tool for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312. Risk of bias was assessed for seven items including: participant selection, representativeness of the trial participants, blinding of participants and study personnel, attrition, missing data, outcomes reporting, and other concerns.

Results of the quality assessment were reported for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 in CS Document B, Appendix D, Section D.3, and for eculizumab trials used in the ITC in CS Document B, Appendix D, Section D.1.4.8. The internal validity and applicability of the ravulizumab trials were also discussed in CS Document B, Section 2.5.

3.1.4.1 Points for critique

The risk of bias tool used is not reflective of the Cochrane Risk of Bias assessment tool (v2.0)[11] but a modified version of an out-of-date prior edition[12] and is not adapted to single-arm trials. The STROBE assessment decisions were not supported by relevant text or specific cross-references, making results difficult to interpret. The CS did not state whether quality assessment was conducted in duplicate. Overall, given these limitations the ERG believes that the CS quality assessment may not be valid.

3.1.5 Evidence synthesis

Results from ALXN1210-aHUS-311 (conducted in complement-inhibitor naïve adult patients) and ALXN1210-aHUS-312 (complement inhibitor treatment naïve and eculizumab experienced children and adolescents) were appropriately not combined in a meta-analysis due to their distinct populations. Results from ravulizumab and eculizumab trials included in the ITC are discussed in sections 3.2 and 3.3, and the ERG critique and summary of the ITC is reported in section 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company systematic review included two multi-centre ongoing single arm open-label trials of ravulizumab, ALXN1210-aHUS-311 and ALXN1210-aHUS-312. Both were described by the company as phase III. ALXN1210-aHUS-311 was conducted in adults with aHUS who are complement inhibitor treatment-naïve, and ALXN1210-aHUS-312 in children and adolescents with aHUS who are complement inhibitor treatment-naïve or clinically stable following ≥90 days treatment with eculizumab. This section provides a summary and critique of each trial.

3.2.1 **ALXN1210-aHUS-311**

3.2.1.1 Design

The study design is summarised in CS Document B, Section B.2.3.1, with further details reported in the clinical study report (CSR).[13] ALXN1210-aHUS-311 is an ongoing single-arm open-label ongoing trial designed to assess the efficacy and safety of ravulizumab in adults with a diagnosis of aHUS who are naïve to complement inhibitor therapy. Patients were recruited across 41 sites in 14 countries ([redacted] patients were recruited in the UK). Participants aged 12 or older were eligible, although enrolment of eligible adolescent patients was deferred to a paediatric trial (Study ALXN1210-aHUS-312). Diagnosis of aHUS was determined by evidence of TMA, haemolysis and kidney injury (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN, haemoglobin, ≤ lower limit of normal [LLN], and serum creatinine level ≥ ULN) without ADAMTS13 deficiency, Shiga toxin, a positive direct Coombs test or systemic bacterial infection. Selection criteria are reported in CS Document B, Table 5.

The study consists of a Screening Period (≤ 7 days), a 26-week Initial Evaluation Period, and an Extension Period, which is planned to "last until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first" (CS Document B, p22 and CSR p28). The first study patient started treatment in March 2017, and data presented by the company runs up to the cut-off date of July 2019, when all patients had at least 52 weeks of follow-up.

Dosages are presented in CS Document B, Table 5. Loading dose was given on Day 1 with maintenance doses on Day 15 and once every eight weeks thereafter by IV infusion. Loading dosages ranged from 2,400mg to 3,000mg and maintenance doses from 3,000mg to 3,600mg based on patient body weight, as per the licence indication. No dose-response studies were conducted for ravulizumab in aHUS.[14] Weight-based dosage was determined by early development studies in healthy volunteers and ongoing Phase 1b and Phase 2 studies in PNH patients (see CSR Section 9.4.4). Discontinuation and retreatment protocols are described in the trial CSR, Section 9.3.3.

The following co-treatments were prohibited at any time after the first dose of study drug for all patients in the study (including those who discontinued ravulizumab but remained in study) until completion of the study or early termination: eculizumab or other complement inhibitors, intravenous immunoglobulin, rituximab, plasma exchange/plasma infusion. Dialysis was permitted, including new dialysis within the first 48-hour period following the first dose of ravulizumab if there was 'a compelling medical need'. Further details are reported in the study CSR, p37.

The primary efficacy endpoint was complete TMA response during the Initial Evaluation Period by central laboratory assessment. Complete TMA response was defined as simultaneous normalization of haematology parameters, which included platelet count and lactate dehydrogenase [LDH] and ≥25% improvement in serum creatinine at two separate assessments obtained at least 28 days apart, and any measurement in-between. All analyses were based on results from a central laboratory.

Secondary endpoints included: time to complete TMA response; complete TMA response status over time; dialysis requirement status at endpoint; observed value and change from baseline in eGFR; CKD stage; observed value and change from baseline in haematological parameters (platelets, LDH, Hb); increase in Hb of ≥ 20 g/L from baseline; change from baseline in QoL (EQ-5D-3L and FACIT-Fatigue). Overall survival was not a pre-specified endpoint, although deaths were captured as a safety outcome. Similarly, major non-renal outcomes (such as cardiac events and thrombosis) were monitored as safety outcomes. Disease recurrence was not a pre-specified outcome; TMA parameters were collected in trial participants, including those who discontinued treatment, although the company stated that no data on recurrence are available yet due the limited follow-up to date. Eligibility for and success of transplantation were not pre-specified endpoints.

The planned sample size was 55. Based on an assumed proportion of Complete TMA response of 65%, the company estimated that 50 patients would yield a 95% confidence interval for the proportion of response with a half-width of approximately 15%; the target sample size was increased to 55 patients to account for drop-out (CS Document B, Table 7 and CSR, Section 16.1).

Methods for dealing with missing data for the primary outcome and its components were reported in CS Document B, Table 7. Patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their last observation carried forward, although when all Complete TMA Response criteria were met, confirmatory result could not be from an assessment that was carried forward from the initial assessment.

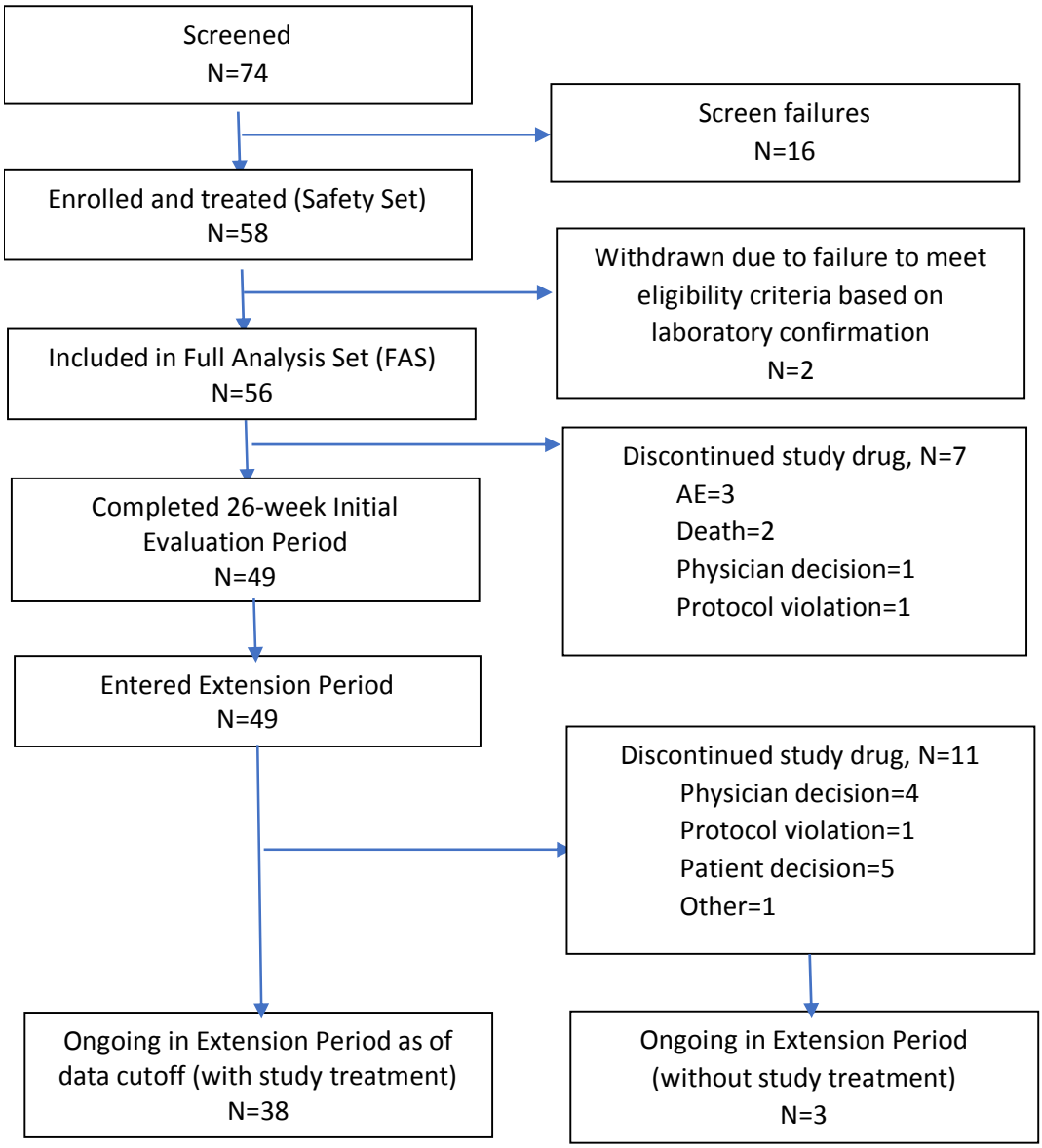
A protocol amendment in July 2017 (four months after treatment of the first study patient was initiated) required that at least 30 patients (rather than the total study population, as initially planned) enrolled met all four TMA requirements at Day 1 (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN,

haemoglobin ≤ LLN, and serum creatinine level ≥ ULN) to ensure that a majority of patients enrolled had abnormal baseline laboratory values.

Out of 74 patients screened, a total of 58 patients were enrolled and received at least one dose of ravulizumab (Safety Set). Two patients from the Safety Set were subsequently excluded for testing positive to Shiga toxin-related HUS. The remaining 56 patients were included in the Full Analysis Set (FAS). The FAS was defined as patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level upper limit of normal (ULN) during screening and no known familial or acquired ADAMTS13 deficiency or STEC-HUS. Of the 56 patients included in the FAS, 49 completed the Initial Evaluation Period.

As of data cut-off (2 July 2019), [redacted] patients are still treated with ravulizumab in the Extension Period, and [redacted] patients continue to be monitored without receiving ravulizumab. Reasons for discontinuation in the Extension Period included physician or patient choice (n=[redacted]), primarily due to complete TMA response and low risk of disease recurrence/relapse (n=[redacted] including [redacted] patients who had onset of TMA post-partum). Following request for clarification, the company reported that [redacted] patients discontinued drug treatment due to physician decision; [redacted] of those were complete TMA responders, [redacted] remained with ESRD, and [redacted] had an alternative non-aHUS diagnosis. Further details are reported in the company's response to points for clarification (PFC), Table 2. A flow diagram is presented in the CSR, Figure 2 and reproduced below in Figure 1.

Figure 1 Flow diagram of trial ALXN1210-aHUS-311 participants as of Data July 2019 cut-off



Source: Adapted from CSR Figure 2, p62.

Points for critique

ALXN1210-aHUS-311 is the only known trial of ravulizumab in an adult aHUS population. Although described as a Phase III clinical trial, study 311 only included 56 patients in its FAS and no comparator arm, and to the ERG's knowledge, no earlier phase trials of ravulizumab in an aHUS population exist. As 311 is a non-comparative trial, it is not designed to assess the relative efficacy and safety of ravulizumab against eculizumab, and the sample size is unlikely to have been sufficient to inform indirect analyses of non-inferiority.

The trial was designed to only include patients who were complement-inhibitor treatment naïve; therefore there is no direct evidence for the efficacy and safety of ravulizumab in patients previously treated with eculizumab. The ERG agree with the company that, as noted in response to PFC, clinicians and patients may want the option of treatment with eculizumab or ravulizumab based on their individual circumstances. However, clinical advisers to the ERG noted that their preference for management of complement-therapy naïve patients in the NHS would almost always involve initiating eculizumab as first-line treatment for approximately three months, until aHUS diagnosis is confirmed, after which patients may switch to ravulizumab. This management strategy is based on the rationale that, due to its shorter half-life, eculizumab is eliminated faster than ravulizumab for those patients who are started on treatment and subsequently receive a non-aHUS diagnosis. The UK advisory board to the company also agreed that nearly all treatment-naïve patients would be initiated on eculizumab and could be considered for treatment switching after 3 months if they were deemed to need long-term therapy, and that "one or two patients" per year with known mutations may be initiated on ravulizumab.[8] There are significant differences in population characteristics between eculizumab treatment-naïve patients and those switching to ravulizumab following response to eculizumab, as shown for instance by the respective baseline characteristics of the treatment naïve and eculizumab experienced cohorts of trial ALXN1210-aHUS-312 (see Table 4). Patients switching to ravulizumab following response to three months of eculizumab therapy will be expected to have their disease stabilized and a confirmed diagnosis of aHUS. This limits the applicability of the adult trial evidence to UK clinical practice.

In the company's response to points for clarification, they noted clinical evidence to support a recommendation of ravulizumab use in adults with aHUS who have received eculizumab for at least 3 months and have evidence of response to eculizumab; this included data from 10 paediatric patients in Cohort 2 of trial ALXN1210-aHUS-312 (described in Table 4 and Section 3.2.2) and data from trial ALXN1210-PNH-302 in PNH patients who were clinically stable following ≥6 months treatment with eculizumab and maintained target complement C5 inhibition and disease control after switching to ravulizumab. Further details are discussed in the company response to PFCs, Section A. The ERG agree that these results are promising. However, as noted by clinical advisers to the ERG, the

paediatric aHUS population and PNH patients are clinically different from adults with aHUS; notably, the paediatric aHUS population has a significantly better prognosis, and PNH patients are a clinically distinct population. Therefore it is uncertain whether the results of trials ALXN1210-aHUS-312 and ALXN1210-PNH-302 may apply to the adult aHUS population.

The screening period of seven days is unlikely to have been sufficient to exclude non-aHUS patients. However, as aHUS diagnosis is challenging and is usually made by ruling out other potential causes of TMA (for example, Shiga toxin-related haemolytic uraemic syndrome [STEC-HUS]); due to this and potential benefits of early initiation of eculizumab therapy, patients in clinical practice may be initiated on complement-inhibitor treatment for aHUS while screening for differential diagnosis continues.[15] Of 58 patients enrolled and treated, two were excluded for testing positive to Shiga toxin-related HUS, which is reflective of clinical practice. As noted in the CS Section B.1.3.2, diagnosis of aHUS is by exclusion and can be challenging. Given this, and due to likely heterogeneity across study centres in participant selection, the ERG is concerned that not all 56 remaining patients included in the FAS may have met the UK criteria for aHUS diagnosis and eligibility for treatment, and that a significant number of patients included in the 311 study may not be reflective of UK patients eligible for complement-therapy. This is further discussed in Section 3.2.1.2.

The trial selection criteria reflected the licence indication and clinical advisers to the ERG considered were broadly acceptable. However, the ERG is concerned that, following a protocol amendment after the start of the study, a large proportion (46%) of participants included in the FAS did not fulfil all four pre-specified TMA criteria at Day 1 of treatment. These patients may have had more favourable prognosis (such as likelihood of complete TMA response at follow-up) compared to patients with TMA at baseline. The company presented subgroup analyses to account for this and showed higher complete TMA results for patients without TMA at Day 1; results are presented in 3.2.3.1.

Clinical advisers to the ERG also noted that the low rate of pathogenic mutation rate observed in the ravulizumab evidence meant that it was not clear that the selection criteria at the discretion of the treating physician were implemented appropriately. Implications are further discussed in Section 3.2.1.2.

The company did not provide evidence on the efficacy and safety of alternative dosing to that described in the licence. The same issue was raised in the EPAR and ERG report for eculizumab. Although at the time of licencing, the company agreed to discuss the feasibility of a further study investigating the efficacy and safety of lower eculizumab doses following approval. The lack of long-term safety evidence for ravulizumab means the risk of long-term safety due to overdosing cannot be excluded. However, clinical advisers to the ERG were not aware of evidence suggesting that lower

doses of ravulizumab may have a better benefit/risk balance, and did not raise any specific concerns due to dosing based on eculizumab safety evidence other than the risk of meningococcal sepsis.

Clinical advisers confirmed that the primary endpoint, although not routinely used in clinical practice, is clinically relevant. The ERG agrees with the company that duration of follow-up is likely to capture a clinically meaningful recovery in the acute phase in aHUS patients following initiation of anti-C5 therapy. Clinical advisers to the ERG noted that recovery in the acute period would be expected in three to six months following treatment initiation if successful; recovery beyond this period would probably not be related to resolution of the original TMA. The follow-up duration to date is insufficient to inform the risk of recurrence following treatment response or long-term safety. The ERG is concerned that the trial Extension Period duration is dependent on registration or approval (in accordance with country-specific regulations) of ravulizumab and may therefore last less than the period required to inform long-term efficacy and safety outcomes. The company did not provide further details and it is not clear whether a NICE approval would affect the duration of the planned Extension Period.

The ERG notes that the lack of a randomised control trial design means that a causal relationship between ravulizumab exposure and complete TMA resolution (or any of the secondary outcomes) cannot be demonstrated. In study 311, observed improvements in renal function or haematological parameters following complement-therapy therapy are not equivalent to a response to treatment. Clinical advisers to the ERG noted that the low rate of pathogenic variants in complement regulation in the 311 trial population suggested that some FAS patients did not have complement-mediated aHUS and may have experienced an improvement in renal function or haematological endpoints due to other factors, such as co-interventions for co-occurring morbidities (e.g. infection, hypertension).

3.2.1.2 Population

Demographic and clinical characteristics of the patients in the FAS of ALXN1210-aHUS-311 are presented in Table 4.

Table 4 Baseline characteristics of patients included in trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (FAS population)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Male, n (%)	19 (33.9)	8 (44.4)	9 (90.0)
Race, n (%)			
White/Caucasian	29 (51.8)	9 (50.0)	5 (50.0)
Asian	15 (26.8)	5 (27.8)	4 (40.0)
Undisclosed	8 (14.3)	1 (5.6)	0
Other	4 (7.1)	4 (22.2)	1 (10.0)
Age at time of first aHUS symptoms		[redacted]	[redacted]
Median years (range)	40.1 (9.3–76.6)		
Age at first infusion of study drug			
Median years (range)	40.1 (19.5–76.6)	[redacted]	12.5 (1.2–15.5)
<2 years, n (%)	0	2 (11.1)	1 (10.0)
2 to <6 years, n (%)	0	9 (50.0)	1 (10.0)
6 to <12 years, n (%)	0	5 (27.8)	1 (10.0)
12 to <18 years, n (%)	0	2 (11.1)	7 (70.0)
18 to <30 years, n (%)	11 (19.6)	0	0
30 to <40 years, n (%)	17 (30.4)	0	0
40 to <50 years, n (%)	15 (26.8)	0	0
50 to <60 years, n (%)	5 (8.9)	0	0
≥60 years, n (%)	8 (14.3)	0	0
Weight at first infusion of study drug	**n=**[redacted]	[redacted]	
Median kg (range)	[redacted]		47.8 (9–69)
<10 kg			[redacted]
10 to <20 kg			
20 to <30 kg			
30 to <40 kg			
40 to <60 kg			
60 to <100 kg			
≥100 kg		[redacted]	
Unknown			
Platelets (normal: 130–400 10^9/L)			281.8
Median x 10^9/L (range)	95.3 (18–473)	51.3 (14–125)	(207–416)
LDH (normal: 120–246 U/L)		1,963	
Median U/L (range)	508 (230–3,249)	(772–4,985)	207 (139–356)
Serum creatinine	n=58[a]	Not available	Not available
Median µmol/L (range)	284 (51–1,027)		
Haemoglobin (normal: 130–175 g/L)			
Median g/L (range)	85 (60.5–140)	74.3 (32–106)	132 (115–148)
eGFR (normal: ≥ 60 mL/min/1.73 m^2)			
Median mL/min/1.73 m^2 (range)	10 (4–80)	22 (10–84)	100 (54–137)

Table 4 continued.	**ALXN1210-aHUS-311 NCT02949128**	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Dialysis within 5 days of first dose n (%)	29 (51.8)	6 (33.3)	0
Kidney transplant prior to enrolment Any transplant, n (%) Related to aHUS, n (%)	8 (14.3)	1 (5.6)	1 (10.0)
Onset of TMA post-partum, n (%)	8 (14.3)		
CKD stage, n (%) 1 2 3A 3B 4 5 Missing	n=54 0 3 (5.4) 1 (1.8) 2 (3.6) 9 (16.1) 40 (71.4) 1 (1.8)		8 (80.0) 1 (10.0) 1 (10.0) 0 0 0 0
Systolic blood pressure, mmHg Median (range)			
Patients with ≥1 known pathogenic variant or autoantibody, n (%) C3 CD46 CFB CFH CFH autoantibody	n=39 8 (20.5) 1 (2.6) 2 (5.1) 1 (2.6) 2 (5.1) 2 (5.1)	n=10 2 (20.0)	Not available
Extra-renal signs or symptoms Cardiovascular, n (%) Pulmonary, n (%) Central nervous system, n (%) Gastrointestinal, n (%) Skin, n (%) Skeletal muscle, n (%)	39 (69.6) 25 (44.6) 29 (51.8) 35 (62.5) 17 (30.4) 13 (23.2)		1 (10.0) 0 0 0 0 0
Medical history prior to study[b], n (%) Hypertension Acute kidney injury Headache Renal failure Nausea Constipation			
PE/PI before first dose of study drug and related to current TMA, n (%)	n=54 48 (82.8)		

Table 4 continued.	**ALXN1210-aHUS-311 NCT02949128**	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Hospitalization history prior to study Emergency room visit, n (%) Other hospitalization, n (%) ICU stay, n (%)	[redacted]	[redacted]	[redacted]
Length of ICU stay N Median days (range)	[redacted]	[redacted]	[redacted]
FACIT-Fatigue score[c] at baseline Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]
EQ-5D-3L score[d] at baseline Mean VAS (SD) Mean TTO (SD)	[redacted]	Not collected	Not collected

Key: aHUS, atypical haemolytic uremic syndrome; C3, Complement 3; CD46, cluster of differentiation 46; CFB, Complement Factor B; CFH, Complement Factor H; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; ICU, intensive care unit; LDH, lactate dehydrogenase; PE, plasma exchange; PI, plasma infusion; SD, standard deviation; TMA, thrombotic microangiopathy, TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], data reported for the safety set; [b], reported in >20% of patients – dashes represent this criteria not being met in individual trials/cohorts; [c], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [d], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.
Sources: ALXN1210-aHUS-311 CSR[13]; ALXN1210-aHUS-312 CSR.[16]; EMA Variation Assessment Report[17]; Rondeau et al. 2020.[18]

Overall, characteristics of the trial 311 population differed from the global aHUS adult cohorts for a number of variables.[19] For instance, the proportion of patients with prior kidney transplant was also significantly lower in study 311 (14.3%) compared with treatment naïve adults in the aHUS registry (26.7%), although patients in study 311 had lower fatigue scores and higher rates of extra-renal signs or symptoms. The median age of patients in study 311 (40.1 years) was somewhat younger than the global treatment naïve population (41.9 years) although this may have limited clinical significance. Comparisons with the global aHUS population are limited by the limited number of variables reported in the aHUS registry (such as kidney disease severity, pathogenic variants) and differences in eligibility criteria.

Points for critique

Most patients initiating ravulizumab would be expected to have undergone prior treatment with eculizumab. TMA parameters (including thrombocytopenia, haemolysis, and kidney injury) in

treatment-naïve adult patients are expected to differ significantly from eculizumab treatment-experienced patients who switch to ravulizumab, as shown in the paediatric trial 312 evidence (Table 4). The absence of eculizumab-experienced patients from study 311 significantly limits the applicability of the study population to the NHS.

The low rate of pathogenic variants in complement regulatory gene/protein mutation or anti-CHF autoantibody in the 311 trial population (20.5%, compared with 45-70% in observational data [20-23] and in eculizumab trial evidence 49–76%)[24-26] suggests that a significant proportion of trial patients included in the FAS may not have aHUS, as noted by clinical advisers to the ERG. The risk of inclusion of non-aHUS patients was potentially even higher in adults, due to a much wider differential diagnosis than in children.

As noted above (Section 3.2.1.1), a significant proportion of patients (46%) enrolled in the FAS did not meet all four TMA requirements at Day 1 (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN, haemoglobin ≤ LLN, and serum creatinine level ≥ ULN). Trial 311 also included severely critically ill patients (including three FAS patients who died) and late presenters (with lower likelihood of renal function recovery) who may not have been eligible for anti-complement therapy based on current NHS practice, as noted by clinical advisers to the ERG. The proportion of patients with prior kidney transplant (14.3%) is also relatively low compared with the trial target (10 to 25 patients) and the global aHUS eculizumab-treatment naïve population (26.7%).[19]

Study 311 included a large proportion of Asian patients, who showed lower rates of complete TMA response in a subgroup analysis (see Section 3.2.3.1). Clinical advisers to the ERG and to the company suggested that these observed differences may be associated with different diagnostic and management strategies rather than ethnic differences, although there is insufficient evidence to confirm this. The company noted that these differences in diagnosis and management may have introduced bias against ravulizumab when compared to UK clinical practice.

Overall, the ERG has a number of concerns about the generalizability of the study 311 population to NHS practice. Interpretations on the direction and magnitude of bias due to differences in population characteristics between trial 311 and the adult aHUS population who would be eligible for ravulizumab in the NHS are difficult to ascertain, due to limited evidence and potentially conflicting or uncertain sources of confounding. The inclusion of a large proportion of patients without TMA at baseline is likely to have positively biased TMA endpoints, as suggested by a subgroup analysis reported in Section 3.2.3.1; on the other hand, the inclusion of severely and critically ill patients that would not have been eligible in NHS practice is likely to have negatively biased ravulizumab efficacy and safety outcomes. Differences in management strategies across trial centres, or the risk that some trial 311 patients did not have aHUS may not necessarily lead to worse efficacy outcomes, contrary to

the discussion in CS Document B, Section 2.13.2.2. Although response to complement-therapy is consistent with an aHUS diagnosis (as response to complement pathway blockade confirms complement medicated aHUS), it is also clinically plausible that improvements in TMA parameters may have been confounded by disease natural history and concomitant therapies for non-aHUS related pathologies (e.g. treatments for infection or hypertension), as confirmed by clinical advisers to the ERG.

3.2.2 ALXN1210-aHUS-312

3.2.2.1 Design

The study design is summarised in CS Document B, Section B.2.3.1, with further details reported in the CSR.[16] ALXN1210-aHUS-312 is an ongoing single-arm open-label ongoing trial designed to assess the efficacy and safety of ravulizumab in children and adolescents with a diagnosis of aHUS. Both eculizumab-treatment experienced and treatment-naïve patients were included. Patients were recruited across 20 sites in eight countries ([redacted] patients were recruited in the UK). Participants aged <18 years were eligible. Patients were split into two cohorts: Cohort 1 were complement-inhibitor therapy naïve, and Cohort 2 included patients who had been treated with eculizumab for at least 90 days prior to screening. For Cohort 2, patients were excluded if they had any known abnormal TMA parameters within 90 days prior to screening.

Diagnosis of aHUS was determined by the same criteria as with trial 311, and there were no restrictions on kidney transplant status or dialysis status, except for patients with chronic dialysis needs who were excluded. Selection criteria are reported in CS Document B, Table 5. Study periods were aligned except for the screening period for Cohort 2 that could continue for up to 28 days. The first study patient started treatment in September 2017, and the latest cut-off data available is December 2019, when all patients had at least 52 weeks follow-up.

Dosages are presented in CS document B, Table 5. Loading doses on Day 1 with maintenance doses on Day 15 and once every eight weeks thereafter for patients weighing ≥ 20 kg, or once every four weeks for patients weighing < 20 kg administered by IV infusion. For Cohort 2 patients, Day 1 occurred 14 days from the patient's last dose of eculizumab. Co-treatment restrictions were broadly aligned with those described in trial 311.

The primary endpoint (complete TMA response) definition was the same as for trial 311, although it was only measured in the treatment-naïve Cohort. Secondary endpoints included Time to complete TMA response and complete TMA response status over time (for Cohort 1) and dialysis requirement status (both Cohorts).

As with trial 311, overall survival was not a pre-specified endpoint, although no deaths were recorded. Similarly, major non-renal outcomes (such as cardiac events and thrombosis) were monitored as safety outcomes. Disease recurrence was not a pre-specified outcome, and no data on recurrence are available yet due the limited follow-up to date. Eligibility for and success of transplantation were not pre-specified endpoints.

In line with trial 311, the FAS population for Cohort 1 included patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level ≥ upper limit of normal (ULN) during screening and had no known familial or acquired ADAMTS13 deficiency or STEC-HUS. The FAS for Cohort 2 included all patients who received at least 1 dose of ALXN1210 and had at least 1 postbaseline efficacy assessment.

The original protocol had a planned sample size of 16 patients. Following a protocol amendment, the total planned sample size was increased to include approximately 23 to 28 patients to account for the addition of Cohort 2. The company stated that this sample size was deemed appropriate to obtain "proper representation in each of the four planned age groups and provide adequate safety information and precision level for the planned estimation." The study protocol provided in response to clarification did not provide further details on how the sample size was derived including any power calculations.

Methods for dealing with missing data for the primary outcome and its components were aligned with those of trial 311 and reported in CS Document B, Table 7.

In Cohort 1, [redacted] patients were screened, enrolled, and treated with ravulizumab (safety set). Of those, three discontinued due to failure to meet eligibility criteria based on laboratory confirmation. The FAS for Cohort 1 included [redacted] patients. [redacted] discontinued treatment due to an AE and the remaining [redacted] completed the Initial Evaluation Period and entered the Extension Period. Of those, one patient discontinued due to physician decision and follow-up of remaining [redacted] was still ongoing as of the latest data cut-off. A flow diagram is presented in the trial CSR, Figure 2. Ten patients from Cohort 2 were screened, enrolled, and treated with ravulizumab in the study, and all 10 patients completed the Initial Evaluation Period and were ongoing in the Extension Period as of the December 2019 cut-off date. Hence the total number of patients included in the FAS was 28.

Points for critique

ALXN1210-aHUS-312 is the only known trial of ravulizumab in a paediatric aHUS population. Although described as a Phase III clinical trial, study 312 only included 28 patients in its FAS and no comparator arm, and no earlier phase trials in children with aHUS exist. Like trial 311, it is not

designed to assess the relative efficacy and safety of ravulizumab against eculizumab, and the sample size is unlikely to have been sufficient to inform indirect analyses of non-inferiority.

As discussed in 3.2.1.1, there is no evidence for the use of alternative dosing of complement-therapy in aHUS. A clinical adviser to the ERG noted there was insufficient evidence to support the use of a full adult dose for patients above 40kg, or for a more flexible approach to dosing and infusion frequency in the paediatric population.

3.2.2.2 Population

Demographic and disease characteristics of patients included in trial 312 are presented in Table 4.

Eculizumab experienced patients enrolled in Cohort 2 had laboratory values within normal ranges at baseline and normal kidney function, whereas treatment-naïve patients included in Cohort 1 had laboratory values outside of normal ranges at baseline and significantly impaired kidney function. Just three patients did not fall under the marketing authorization due to their low weight (under <10 kg).

Points for critique

As with trial 311, trial 312 included a lower proportion of patients with a known pathogenic variant or autoantibody than expected in UK clinical practice. Therefore, there is a risk that a significant number of patients included in trial 312 did not have aHUS.

Trial 312 included a minority (37%) of patients with experience of eculizumab therapy before switching to ravulizumab. As with adults, clinical advisers to the ERG expect that most paediatric aHUS patients would receive eculizumab as first-line prior to switching to ravulizumab, with the exception of some children for whom it may be hard to maintain central lines for long periods of time and who may be preferred for ravulizumab treatment as first-line. The fact that most patients included in the FAS were eculizumab treatment-naive limits the generalisability of the trial population to the aHUS population who would receive ravulizumab in the NHS.

3.2.3 Effectiveness

3.2.3.1 ALXN1210-aHUS-311

Efficacy results for the FAS population of ALXN1210-aHUS-311 during the Initial Evaluation Period (26 weeks) and Extension Period (available up to 2 July 2019 when all participants had received at least 52 weeks of treatment) are presented in CS Document B Table 8, and reproduced in Table 5 below. The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks).

Table 5 Summary of efficacy results from ALXN1210-aHUS-311: Initial Evaluation and Extension Period (up to 2 July 2019 cut-off) (FAS)

	Initial Evaluation Period	Extension Period
Complete TMA response, n (%) [95% CI]	30 (53.6) [39.6–67.5]	[redacted]
Platelet count normalization, n (%) [95% CI]	47 (83.9) [73.4–94.4]	[redacted]
Change in platelet count, Median x10^9/L (range)	125 (-126, 338)	Day 407 [redacted]
LDH normalization, n (%) [95% CI]	43 (76.8) [64.8–88.7]	[redacted]
Change in LDH, Median U/L (range)	-310.8 (-3,072, 9)	Day 407 -[redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	33 (58.9) [45.2–72.7]	[redacted]
Haematologic normalization[a], n (%) [95% CI]	41 (73.2) [60.7–85.7]	[redacted]
Haemoglobin response[b], n (%) [95% CI]	40 (71.4) [redacted]	[redacted]
Change in haemoglobin, Median g/L (range)	35 (9, 69)	Day 407 [redacted]
Time to complete TMA response, median days (95% CI)	86.0 [redacted]	NR
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	[redacted]	**Day 407** [redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	29 (-13, 108)	Day 407 [redacted]
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline, n/N (%)	17/29 (58.6) 6/27 (22.2)[c]	[redacted]
CKD stage improvement, n/N (%)	32/47 (68.1)	[redacted]
CKD stage worsening, n/N (%)	2/47 (4.3)	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	20.0 (-16, 48) [redacted]	Day 351 [redacted]
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	37/44 (84.1)	Day 351 [redacted]
Change in EQ-5D-3L score[e], Mean VAS (SD) (IEP: n=45; EP: n=41) Mean TTO (SD) (IEP: n=46; EP: n=42)	[redacted]	[redacted]

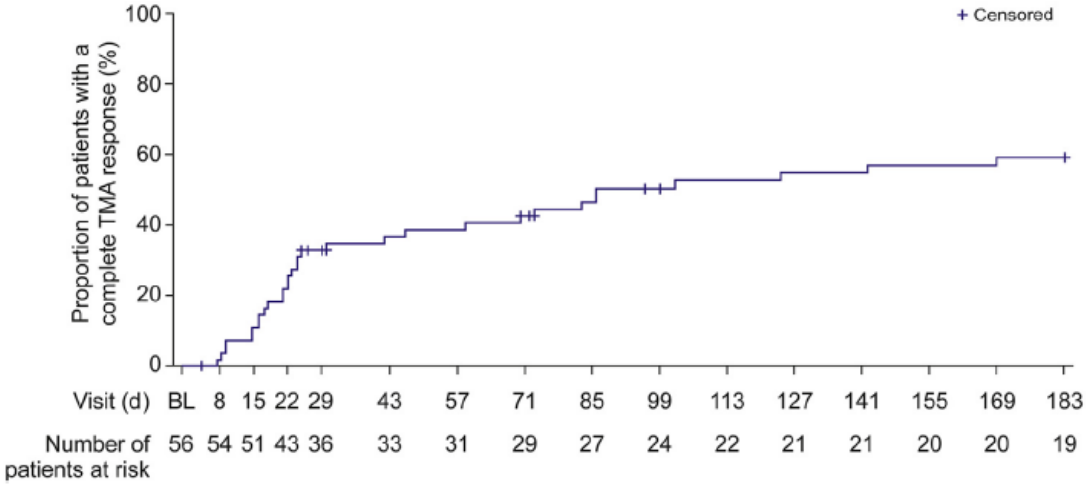
Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.

	Initial Evaluation Period	Extension Period
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], one additional patient initiated and discontinued dialysis within the Initial Evaluation Period; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [e], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.		

Complete TMA response

Complete TMA response was attained by 53.6% (95% CI 39.6 to 67.5) of patients in the Initial Evaluation Period, in a median time of 86 days ([redacted]); Figure 2 shows that the number of patients with a complete TMA response continued to increase over time during the Initial Evaluation Period, although most complete TMA responses were observed between day 7 and 29 approximately. [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off (2 July 2019), making a total of [redacted] (95% CI [redacted] of patients attaining complete TMA response. As noted above (Section 3.2.1.1), it is unlikely that these later events are directly related to complement inhibition.

Figure 2 Kaplan–Meier plot of time to complete TMA response in ALXN1210-aHUS-311: Initial Evaluation Period (FAS)



Key: BL, baseline; d, day; FAS, full analysis set; TMA, thrombotic microangiopathy.
Notes: Patients who did not have a response were censored on the day of their last study visit or at study discontinuation.
Source: CS Document B, Figure 5.

Subgroup analysis results for the primary endpoint are reproduced in Figure 3 below. It does not appear that any of these subgroups were pre-specified. The subgroup analysis results show notably higher rates of complete TMA response in patients treated in Europe, and in patients without kidney

transplant history, although the small number of patients and overlapping confidence intervals mean that these results may not be reliable.

Figure 3 Forest plot of cTMA response rate in subgroups of ALXN1210-aHUS-311: Initial Evaluation Period

Source: CS Document B, Appendix E, Figure 5.

Renal endpoints

Renal function improvement (≥25% reduction in serum creatinine from baseline) was observed in 59% of patients in the Initial Evaluation Period, and by [redacted] in the Extension Period. A median increase of 29 mL/min/1.73 m^2 in the estimated glomerular filtration rate (eGFR) from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m^2 at day 407. CKD stage improvement was observed in 68% of patients in the Initial Evaluation Period and [redacted] in the Extension Period, and two participants had worsening in CKD stage (from stage 4 to 5) during the Initial Evaluation Period. CKD stage shift from baseline in the Initial Evaluation and Extension Periods are presented in CS Document B, Table 9 and 13 respectively.

Of the patients on dialysis at baseline, 59% discontinued renal replacement therapy (RRT) during the Initial Evaluation Period and [redacted] in the Extension Period; 22% of those without dialysis at baseline initiated RRT during the Initial Evaluation Period, [redacted] during the Extension period.

Haematological endpoints

Seventy-three percent of participants achieved haematological normalization; 84% of patients had platelet count normalization during the Initial Evaluation Period, and [redacted] during the extension period. LDH normalisation was achieved by 77% in the Initial Evaluation Period, and by [redacted] in the Extension Period. Further details are reported in Table 5.

Health-related quality of life (HRQL)

Fatigue scores were measured using the FACIT-Fatigue scale, ranging from 0 to 52, with a maximum score indicating no fatigue, and with improvements of ≥3 considered to be clinically meaningful.[27] Of the 44 patients with FACIT-Fatigue data at baseline and at the end of the Initial Evaluation Period, 84% reported a ≥3-point improvement in FACIT-Fatigue score, and a mean improvement of [redacted] was observed during the Initial Evaluation Period. Clinically significant improvements in EQ-5D-3L scores from baseline were recorded and are reported in Table 5.

Overall mortality, disease recurrence, major non-renal outcomes, eligibility for/success of transplantation

Overall survival was not reported as an efficacy outcome but deaths were reported as part of the safety assessment. Similarly, major non-renal clinical outcomes such as thrombosis or cardiac events were captured as safety events. The CS stated that no data on disease recurrence are available yet due to limited follow-up to date. Eligibility for/success of transplantation was not captured in the ravulizumab trials. Data on drug resistance is reported in the safety results section.

Points for critique

Results from trial 311 provide promising evidence that ravulizumab may be effective for the management of complement-therapy naïve adult patients with aHUS. Improvements in renal function observed at 26 weeks follow-up were generally maintained at the latest data cut-off.

Due to significant limitations in the design of the study, the ERG has a number of concerns about the generalisability of the trial results to NHS clinical practice. All patients included in trial 311 were complement-therapy naïve, where it is expected that nearly all patients who would be likely to receive ravulizumab in clinical practice would have received eculizumab as first-line treatment. Due to challenges and likely heterogeneity in patient selection across study centres, and notably the relatively low prevalence of pathogenic variants in the trial population, the ERG is concerned that a significant number of patients included trial 311 may not have had aHUS.

Given the small sample size and as evidenced by the large confidence intervals in most of the efficacy endpoints reported, the precision of efficacy estimates is uncertain. In addition, the lack of randomised design and concerns about inclusion of non-aHUS patients mean that the causal relation between

ravulizumb exposure and observed clinical outcomes is largely uncertain. The likely direction and magnitude of bias associated with these limitations are too uncertain to predict. Lack of blinding means that self-reported HRQL outcomes should be interpreted with caution.

3.2.3.2 ALXN1210-aHUS-312

Efficacy results for the FAS population of ALXN1210-aHUS-312 during the Initial Evaluation Period (26 weeks) and Extension Period when all participants had received at least 52 weeks of treatment are presented in CS Document B Tables 8 and 12, and reproduced in Table 6 below. The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks) for Cohort 1, and [redacted] weeks (range: [redacted]) for Cohort 2.

Table 6 Summary of efficacy results from ALXN1210-aHUS-312: Initial Evaluation and Extension Period (up to 3 December 2019 cut-off) (FAS)

	Initial Evaluation Period		Extension Period	
	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Complete TMA response, n (%) [95% CI]	14 (77.8) [52.4–93.6]	Not relevant	[redacted]	Not relevant
Platelet count normalization, n (%) [95% CI]	17 (94.4) [72.7–99.9]	Platelet count remained stable	[redacted]	[redacted]
Change in platelet count, Median x10^9/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
LDH normalization, n (%) [95% CI]	16 (88.9) [65.3–98.6]	LDH remained stable	[redacted]	[redacted]
Change in LDH, Median U/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	[redacted]	Not relevant	[redacted]	Not relevant
Haematologic normalization[a], n (%) [95% CI]	16 (88.9) [65.3–98.6]	Not relevant	[redacted]	Not relevant
Haemoglobin response[b], n (%) [95% CI]	16 (88.9) [65.3–98.6]	Hb remained stable	[redacted]	[redacted]
Change in haemoglobin, Median g/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
Time to complete TMA response, median days (95% CI)	[redacted]	Not relevant	Not applicable	Not relevant
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	108 [redacted]	[redacted]	**Day 407** [redacted]	**Day 351** [redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	80 [redacted]	[redacted]	Day 407 [redacted]	Day 351 [redacted]

Table 6 continued.				
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline, n/N (%)	[redacted]	Not relevant [redacted]	[redacted]	Not relevant [redacted]
CKD stage improvement, n/N (%)	15/17 (88.2)	[redacted]	[redacted]	[redacted]
CKD stage worsening, n/N (%)	0/17 (0.0)	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	10.0 [redacted]	[redacted]	**Day 351** [redacted]	**Day 351** [redacted]
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	[redacted]	Not relevant	Day 351 [redacted]	Not relevant
Change in EQ-5D-3L score[e],	Not collected	Not collected	Not collected	Not collected

Key: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], one additional patient initiated and discontinued dialysis within the Initial Evaluation Period; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [e], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.

Complete TMA response

Cohort 1

Complete TMA response was attained by 78% (95% CI 52 to 94) of patients in the Initial Evaluation Period, in a median time of [redacted] days; Figure 2 shows that the number of patients with a complete TMA response outcome increased over time during the Initial Evaluation Period. [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off, making a total of [redacted] (95% CI [redacted]) complete TMA response rate.

Renal endpoints

Cohort 1

Renal function improvement (≥25% reduction in serum creatinine from baseline) was observed in [redacted] of patients in the Initial Evaluation Period, and by [redacted] in the Extension Period. A median increase of 80 mL/min/1.73 m^2 in eGFR from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m^2 at day 407. CKD stage improvement was observed in 88% of patients in

the Initial Evaluation Period and [redacted] in the Extension Period, and no patients had worsening in CKD stage. CKD stage shift from baseline in the Initial Evaluation and Extension Periods are presented in CS Document B, Table 10 and 14 respectively.

Of the patients on dialysis at baseline, [redacted] discontinued dialysis during the Initial Evaluation Period and [redacted] in the Extension Period. [redacted] patients initiated dialysis during the study periods in either cohort.

Cohort 2

Renal function remained mostly stable in patients switching from eculizumab to ravulizumab, although [redacted] during the Initial Evaluation period. [redacted]

Haematological endpoints

In Cohort 1, 89% of participants achieved haematological normalisation, 94% had platelet count normalisation, and 89% had LDH normalisation during the Initial Evaluation Period. In Cohort 2, haematological endpoints remained stable overall. Further details are reported Table 6.

HRQoL

In Cohort 1, [redacted] (of [redacted] patients) reported a ≥3-point improvement in FACIT-Fatigue score, and a mean improvement of [redacted] points was observed during the Initial Evaluation Period. EQ-5D scores were not collected.

Overall mortality, disease recurrence, major non-renal outcomes, eligibility for/success of transplantation

Trial 312 reported no deaths. Similarly to study 311, major non-renal clinical outcomes were captured as safety events, no data on disease recurrence are available yet due to limited follow-up to date, and eligibility for/success of transplantation was not captured. Data on drug resistance is reported in the safety results section.

Points for critique

Results from trial 312 provide promising evidence that ravulizumab may be effective for the management of complement-therapy naïve and eculizumab experienced paediatric patients with aHUS. As with trial 311, improvements in renal function in eculizumab-naïve patients observed at 26 weeks follow-up were generally maintained at the latest data cut-off.

The precision of efficacy estimates in both trial cohorts is uncertain, as evidenced by the large confidence intervals in most of the efficacy endpoints reported. In addition, the lack of randomised design and concerns about inclusion of non-aHUS patients mean that the causal relation between

ravulizumb exposure and observed clinical outcomes is largely uncertain. As with trial 311, the likely direction and magnitude of bias associated with these limitations are too uncertain to predict. Lack of blinding means that self-reported HRQL outcomes should be interpreted with caution.

3.2.4 Safety

Table 7 presents a summary of safety results as of the latest available data cut-off for ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

Table 7 Summary of adverse events from ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (Safety Populations, Extension Period as of December 2019 cut-off dates)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Ravulizumab Cohort 2 (n=10)
Patients with any AE, n (%)	[redacted]	[redacted]	[redacted]
Common adverse events[a], n (%)	[redacted]	[redacted]	[redacted]
Headache	[redacted]		
Diarrhoea			
Vomiting	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
AE severity, n (%)			
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]

Patients with any treatment-related AE, n (%)	[redacted]	[redacted]	[redacted]
Patients with any serious adverse event, n (%)	[redacted]	[redacted]	[redacted]
Common SAEs[b], n (%) Hypertension Pneumonia Malignant hypertension Urinary tract infection Septic shock aHUS Viral gastroenteritis Abdominal pain	[redacted]	[redacted]	[redacted]
Meningococcal infections, n (%)	[redacted]	[redacted]	[redacted]
Discontinuation due to AE, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Death due to AE, n (%)	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; aHUS, atypical haemolytic uremic syndrome; SAE, serious adverse event.
Notes: [a], Defined as ≥ 15% of patients – dashes represent events not meeting these criteria in individual trials/cohorts; [b], Defined as >1 patient – dashes represent events not meeting these criteria in individual trials/cohorts.

3.2.4.1 ALXN1210-aHUS-311

[redacted]

AEs deemed to be treatment-related were assessed by the study investigator, and the CS did not report that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel. In response to clarification, the company stated that their UK advisory group had reviewed death narratives based on short summaries.

Four patients died during the study (three patients from the FAS and one from the safety analysis set). Table 4 presents of summary of the four deaths. Following request for clarification, the company provided narratives for deaths and serious adverse events from the CSR to the ERG. The three deaths from the FAS resulted from a fatal treatment-emergent AE; two patients died from a septic shock and one from a cerebral haemorrhage. The other death occurred in a patient who had been discontinued from the study after a single dose of ravulizumab following differential diagnosis (positive STEC test) from a cerebral artery thrombosis. All four patients had significant comorbidities and were critically ill at treatment initiation; three (including two FAS patients) were receiving mechanical ventilation at baseline and two patients were receiving antibiotics for an existing infection.

The company concluded that the four deaths were unrelated to ravulizumab, as per the CSR and the trial publication.[13, 18] This view differs from the conclusions of the company's UK advisory board (ref. 24 in CS Document B, page 160) which stated that it was "difficult to draw any definitive conclusion from the data presented and not possible to say with certainty that these deaths were not treatment-related." Clinical advisers to the ERG also agreed that it was not possible to conclude with certainty that these deaths were not treatment-related, although they concurred with the company that, given their presentation at baseline, these patients may not have had aHUS and would likely not have been treated with ravulizumab in UK clinical practice.

Table 8 Summary of deaths in patients treated with ravulizumab in ALXN1210-aHUS-311 (from CS Document B, Appendix F, Table 23)

Cause of death	**Age**	**Time on treatment**	**Key timepoints**
Septic shock	73	Onset of event Day 2 Patient received 1 dose Death on Day 3	**Prior to the first dose:** history of diabetes, coronary heart disease, congestive heart failure. Recent ischemic stroke, encephalopathy, respiratory failure, and on multiple antibiotics for infection. **On day of the first dose:** receiving mechanical ventilation, *pseudomonas* in pulmonary aspirate. **Additional points:** CRP and white cell count were elevated prior to ravulizumab treatment and clotting assays were normal. No genetic analysis was performed.
Septic shock	76	Onset of event Day 6 Patient received 2 doses Death on Day 25	**Prior to the first dose:** history of diabetes, kidney transplant in 2010 (kidney disease due to diabetes), myelofibrosis (cytopenia) diagnosed in 2016. Recent shock (septic or hypovolemic), acute respiratory distress syndrome, multiple infections (*Pneumocystis carinii* and CMV pneumonia). Patient was on antibiotics, cardiovascular medications, insulin, sirolimus, prednisolone and inotropes. **On day of the first dose:** receiving mechanical ventilation. **Day 6:** new septic shock due to *Corynebacterium* and *Candida lusitaniae* in the catheter (tip taken for culture prior to the first dose). **Additional points:** clotting assays were normal prior to ravulizumab treatment, while CRP was elevated, and white cell count low. No pathogenic variant found.
Cerebral haemorrhage	46	Onset of event Day 93 Patient received 3 doses Death on Day 107	**Prior to the first dose:** uncontrolled hypertension (multiple drugs); Stage 4 CKD >2 months that had progressed to CKD Stage 5, requiring dialysis at initiation of study drug; thrombocytopenia; anaemia; and hypercalcemia. **Day 93:** patient experienced headache, nausea, vomiting, left side weakness and dysarthria, and was admitted with loss of consciousness. Right intraventricular haemorrhage and intracranial haemorrhage were identified. Following surgery, the patient was transferred to neurosurgery ICU. However, hypertension and loss of consciousness persisted, and supportive care was withdrawn. No pathogenic variant found.

Table 8 continued.

Cerebral artery thrombosis	77	Onset of event prior to treatment Patient received 1 dose but was excluded from efficacy analysis due to positive *Shiga* toxin test Death on Day 15	**Prior to the first dose:** in ICU for cerebral arterial thrombosis and seizures. **On day of the first dose:** receiving mechanical ventilation. **Additional points:** white cell count and CRP were elevated prior to ravulizumab treatment. Seizures and cortical infarcts approximately 10 days later, supportive care was withdrawn. No genetic analysis was performed.

Key: ARDs, acute respiratory distress syndrome; CKD, chronic kidney disease; CMV, cytomegalovirus; CRP, C-reactive protein; ICU, intensive care unit.
Source: Rondeau et al. 2020.[18]

One patient had a treatment-emergent antidrug antibody positive test on Day 68 although there was no apparent impact on safety and efficacy.[13]

Targeted AEs for this study were meningococcal infections. In one country, the targeted AEs also included sepsis, serious infections, *Aspergillus* infection, infusion reactions, serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema.[13, 16]

CS Document B, p.96 states that ravulizumab "could reduce the risk of vein damage" compared with eculizumab. In response to clarification, the company noted that although there are no specific data demonstrating a lower risk of vein damage with ravulizumab compared to eculizumab, long-term intravenous (IV) therapy is associated with complications which include among others, venous depletion over time. [28, 29] The company quoted evidence from a survey of 34 aHUS patients suggesting that venous access was a difficulty with eculizumab for approximately a third or respondents (12/34), and that given the expected significant reduction in number of annual ravulizumab infusions compared to eculizumab, it was reasonable to expect a corresponding reduction in the risks associated with frequent IV infusions.

3.2.4.2 ALXN1210-aHUS-312

Table 7 (Section 3.2.4) presents a summary of safety results as of the latest available data cut-off for ALXN1210-aHUS-312. [redacted] experienced an AE, and [redacted] patient in [redacted] discontinued the study to an AE [redacted] patients died during the study, [redacted] cases of meningococcal infections, and [redacted] treatment-emergent ADA positive samples were observed in [redacted] Treatment related AEs and serious adverse events in Cohort 1 were [redacted] and [redacted] respectively.

As in trial 311, AEs deemed to be treat-related were assessed by the study investigator, and it does not appear that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel.

Points for critique

AEs deemed to be treatment-related were assessed by the study investigators, and the CS did not report that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel. Due to the absence of data beyond the 2019 cut-off, the long-term safety of ravulizumab is uncertain. As meningococcal infections were the only targeted adverse event except in one country, the risk that other serious infection may not have been captured cannot be excluded.

The ERG believes that in view of the evidence provided, it is not possible to conclude whether the deaths recorded in trial 311 were not treatment-related, although the ERG agrees with the company that it is likely that the patients who died would not have been eligible for ravulizumab in NHS practice.

The ERG agrees with the company that is clinically plausible that the reduced need for infusions with ravulizumab may be associated with a lower risk of infusion-related adverse events compared with eculizumab; there is currently no evidence to support this.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Due to the lack of direct evidence comparing ravulizumab with eculizumab, the company conducted indirect treatment comparison (ITC) analyses. Since both treatments were developed by the company, the ERG judged it unlikely that any relevant comparator data were missed. Clinical advisors to the ERG confirmed that eculizumab was the only relevant comparator.

3.3.1 Summary of included studies

Five single arm trials were included in the ITC (see Table 9).

Table 9 Single arm trials of ravulizumab and eculizumab in aHUS patients included in the ITC analyses*

Trial ID	Population	Sample size	Treatment	Mutation and/or auto-antibodies identified
ALXN1210-aHUS-311	Complement Inhibitor naïve adults	N=58	Ravulizumab	8/39 (20.5%)
ALXN1210-aHUS-312	Complement Inhibitor naïve children and adolescents	N=21	Ravulizumab	9/10 (90%)
aHUS-C08-002	Complement Inhibitor naïve and plasma therapy-resistant	N=17 (n=16 adults, n=1 adolescents)	Eculizumab	13/17 (76%)
aHUS-C10-003	Complement inhibitor naïve paediatric patients	N=22	Eculizumab	11/22 (50%)
aHUS-C10-004	Complement Inhibitor naïve adults	N=44	Eculizumab	20/41 (49%)

*Adapted from CS Document B, Table 16, and company response to question A10 of PFCs

Points for critique

Limited evidence

All evidence included in the ITC analyses were from single arm trials with relatively small sample sizes. The ERG considers that the company have made adequate justification for including these sources of evidence. However, there are substantial uncertainties when evaluating the comparative effectiveness of ravulizumab and eculizumab that are inherent to single arm trials with small sample sizes. Without randomized controlled trials, it is not possible to rule out the impact of confounding on comparisons between these treatments (see section 3.4.1 for further details on the potential impact of confounding). In addition, the trials were not designed to test whether ravulizumab and eculizumab are similar in effectiveness. The sample sizes of these trials are unlikely to be large enough to draw firm conclusions on comparative effectiveness (see section 3.4.2 for further details).

Comparability of trials at baseline

The ERG identified several important concerns regarding the comparability of the eculizumab and ravulizumab trials. There is a substantial possibility that the population recruited in one of the ravulizumab trials is different from that recruited in the eculizumab trials. Moreover, standard practice may have differed between centres in the ravulizumab trial which raises further issues in comparisons with eculizumab. These uncertainties are summarised below.

First, there was a substantial difference of pathogenic variants (20.5%) for ravulizumab patients recruited in the ALXN1210-aHUS-311 study compared with the eculizumab trials (aHUS-C10-003: 70%, aHUS-C10-004: 49%).[24, 26] Because aHUS is a diagnosis of exclusion, there is a risk that patients with similar symptoms but alternative conditions will be recruited to trials. The low mutation rate suggests this may have been the case with the ravulizumab trial.[30]

Second, the definition of aHUS was more restrictive 10 years ago when the eculizumab trials were conducted.[30] Therefore, patients recruited to the current ravulizumab trials using broader definitions of aHUS are likely to differ from patients in eculizumab trials recruited according to earlier definitions.

Third, there were important differences between treatment centres recruited to the ravulizumab (20-29% of patients were recruited in Taiwan, Japan and South Korea) and eculizumab (no patients were recruited in Asia) trials. Data from the ravulizumab trials suggests treatment may have differed between Asian and non-Asian treatment centres. All patients recruited outside Asia were treated

within 4 weeks from the start of the TMA episode. However, 11/14 patients treated in Asia received treatment at least 4 weeks after the start of the current TMA episode.[30]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Matching of baseline patient characteristics

The company conducted prognostic score matching using stabilized weights to reduce baseline differences observed between the ravulizumab and eculizumab trials.

Since the company had access to individual patient data for all included trials, they combined all trial data into one dataset and conducted separate analyses for adult non-transplant, adult transplant, and paediatric patients (see Table 10).

Table 10 Baseline differences between ravulizumab and eculizumab prior and after application of stabilized weighting*

	Adult non-transplant patients		**Adult transplant patients**		**Paediatric patients**	
Outcomes	**Ravulizumab**	**Eculizumab**	**Ravulizumab**	**Eculizumab**	**Ravulizumab**	**Eculizumab**
Dialysis status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients recruited in Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of patients aged 65 years or over	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age in years: mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*sample sizes quoted for all data reported after application of stabilized weights refer to effective sample size (ESS), SD= standard deviation, n=sample size, eGFR=estimated Glomerular Filtration Rate

Points for Critique

Dialysis status and eGFR values

Dialysis status at baseline and eGFR values were identified by clinical advisers to the ERG as key prognostic factors (company analyses concur). Prognostic score matching generally reduced imbalances in dialysis status at baseline and eGFR values between ravulizumab and eculizumab trials in adult non-transplant and paediatric patients. Although there may have been baseline differences for these measures in transplant patients, it is difficult to tell the impact of these imbalances given the small numbers in this population [redacted]

Pathogenic variant or autoantibody rates

It is well accepted that the course of aHUS is impacted by the presence of genetic variants. Therefore, the low mutation rate (20.5%) for adult ravulizumab patients compared with mutation rates in the eculizumab trials is a major limitation of the ALXN1210-aHUS-311 study. The proportion of genetic variants identified in the adult eculizumab trials (aHUS-C10-004= 49%; aHUS-C08-002=76%)[24, 26] is similar to that found in the wider literature and in aHUS patients currently treated in the NHS (69%)[5] (see Table 9). As discussed above, commentaries in the literature[30] and clinical advice provided to the ERG raise important questions on whether a substantial proportion of patients included in this ravulizumab trial were correctly diagnosed with aHUS.

Despite the potential importance of these differences between trials, the company did not address these in their ITC analyses. In response to question A10 in points for clarification (PFCs), the company provided two main justifications:

- genetic analyses were not mandatory in the ravulizumab trials (39/56 (70%) patients received genetic testing)
- the company's clinical advisers did not consider genetic variants or autoantibodies to be an important prognostic factor
- genetic analysis has moved on since the eculizumab trials therefore a 'like-for-like' comparison is not possible

The ERG judged this justification to be insufficient. First, it has been pointed out that genetic testing is standard practice for many treatment centres, therefore it is likely the company could have obtained most of these missing data on genetic variants by contacting treatment centres.[30] Even if it was not possible to obtain these genetic data, matching could have been conducted in patients with available data for this covariate in a similar way to other prognostic factors included in the ITC analyses. Alternatively, the impact of including this factor in the matching analyses could have been assessed in sensitivity analyses.

The second justification provided by the company was also considered insufficient. Clinical advice to the ERG highlighted substantial differences in proportion of patients with genetic variants between eculizumab and ravulizumab trials as one of the major uncertainties of the ITC analyses.

The ERG noted several issues with the third justification. First, this reasoning is not applied consistently across the submission. As noted above, various aspects of practice (e.g. diagnosis of aHUS) have changed since the eculizumab trials but this did not prevent the company from comparing ravulizumab with these eculizumab trials. Second, although the ERG accepts that genetic analyses have developed over time, the company did not provide evidence that changes in genetic analyses would substantially impact comparisons of pathogenic variants/autoantibody rates across trials. Pathogenic variants/autoantibody rates in the eculizumab trials were similar to that reported in current UK clinical practice.

Patients recruited in Asia

In adult non-transplant patients, the proportion of patients recruited in Asia was higher in ravulizumab than eculizumab ([redacted] trials. The difference was slightly larger when applying stabilized weights [redacted] Similar imbalances were observed in adult transplant and paediatric patient populations. Sensitivity analyses excluding patients recruited in Asia are considered in section 3.4.2.

Age

In adult non-transplant patients, mean age was higher for ravulizumab patients compared with eculizumab patients both prior to weighting ( ) and after application of stabilized weights ( ). Similar baseline imbalances were observed for adult transplant patients. Sensitivity analyses excluding patients 65 years and over are considered in section 3.4.2.

Other

Additional baseline differences between ravulizumab and eculizumab for adult transplant patients were identified for gender (after application of stabilized weights, ravulizumab patients were much more likely to be male: and systolic blood pressure (after application of stabilized weights, eculizumab patients had much higher systolic blood pressure**:**). Systolic blood pressure differences are potentially important as this factor was identified as a potential confounder by clinical advisers to the company. But it is difficult to predict what magnitude and direction of bias would be expected from these baseline differences.

3.4.2 Results of Indirect Comparison

Table 11 Summary of aHUS related outcomes in adult non-transplant, adult transplant, and paediatric patients*

	Adult non-transplant patients		**Adult transplant patients**		**Paediatric patients**	
Outcomes	**Ravulizumab (ESS=46)**	**Eculizumab (ESS=39)**	**Ravulizumab (ESS=9.3)**	**Eculizumab (ESS=12.7)**	**Ravulizumab (ESS=10.7)**	**Eculizumab (ESS=21.3)**
Change in CKD stage: Improved Unchanged Worsened						
eGFR, mean (SD)						
Dialysis at endpoint						
cTMA response						
Improvement in creatinine						
Platelet count normalisation						
LDH normalisation						
Haematological normalisation						
EQ-5D VAS, mean (SD)						

FACIT-fatigue, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died in trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ESS= effective sample size, SD=standard deviation, eGFR=estimated Glomerular Filtration Rate

* Adapted from CS Document B, Tables 21 and 22

Results from the ITC analyses are summarised in Table 11. The CS concluded that there were no statistically significant or clinically relevant differences in effectiveness between ravulizumab and eculizumab.

Completed TMA (cTMA) response

Meeting criteria for cTMA response was less likely for adult non-transplant patients ([redacted]) receiving ravulizumab compared with eculizumab, but more likely in adult transplant patients ([redacted] and paediatric non-transplant patients ([redacted]

Renal endpoints

Adult transplant ([redacted] and adult non-transplant ([redacted] patients receiving ravulizumab were less likely than patients receiving eculizumab to experience an improvement in CKD stage. A similar proportion of ravulizumab ([redacted]) and eculizumab ([redacted]) paediatric non-transplant patients experienced an improvement in CKD stage.

There may also be differences between ravulizumab and eculizumab for patients requiring dialysis at endpoint. There was an approximately [redacted] increased risk for requiring dialysis at endpoint for ravulizumab compared with eculizumab in adult non-transplant patients ([redacted] ravulizumab vs eculizumab [redacted]). Paediatric non-transplant populations receiving ravulizumab were also more likely to require dialysis at endpoint ([redacted]) However, less ravulizumab patients in the adult transplant population required dialysis at endpoint ([redacted]

Haematological endpoints

Haematological (ravulizumab [redacted] vs eculizumab [redacted] LDH (ravulizumab [redacted] vs eculizumab [redacted]), and platelet count (ravulizumab [redacted] vs eculizumab [redacted] normalization rates were higher for eculizumab in non-transplant populations.

Haematological (ravulizumab [redacted] vs eculizumab [redacted] and LDH (ravulizumab [redacted] vs eculizumab [redacted]) normalisation rates were slightly higher in eculizumab transplant patients. In paediatric non-transplant

patients, haematological (ravulizumab [redacted] vs eculizumab [redacted]) and LDH (ravulizumab [redacted] vs eculizumab [redacted]) normalization rates were higher for ravulizumab. Platelet count normalisation rates were [redacted] for all transplant and paediatric non-transplant patients.

Quality of life

Ravulizumab patients reported [redacted] fatigue than eculizumab in adult non-transplant and transplant patients. While in paediatric non-transplant patients fatigue was [redacted] in both groups. [redacted] quality of life (EQ-5D VAS) was reported for ravulizumab in non-transplant patients but [redacted] quality of life for eculizumab in transplant patients.

Deaths

The ITC analyses included data from the full analysis set (FAS), where there were [redacted] deaths in non-transplant patients receiving ravulizumab. As discussed in more detail in section 3.2, the safety population included [redacted]. No deaths were reported in the eculizumab trials. Although this evidence may be of limited generalisability to the UK, differences regarding the safety of ravulizumab in comparison with eculizumab cannot be ruled out.

Sensitivity analyses

Sensitivity analyses excluding patients recruited in Asia, reduced differences between eculizumab and ravulizumab for most outcomes. However, ravulizumab patients were still [redacted] as likely to need dialysis at endpoint compared with eculizumab patients ([redacted]**).** Excluding patients 65 years or over had less of an impact on results.

Non-inferiority trial of ravulizumab vs eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH)

In addition, to the data in aHUS patients, the CS also pointed out a trial in patients with PNH found that ravulizumab met criteria for non-inferiority with eculizumab across a range of outcomes (see CS section B2.13.2.1 for further discussion).

3.4.2.1 Points for Critique

The ERG accepts the company's argument that non-inferiority trials were not feasible in aHUS patients. However, the lack of a non-inferiority trial means that, although it is biologically plausible ravulizumab and eculizumab are associated with similar clinical effectiveness, this remains uncertain despite being a key assumption of the submission.

The CS states, "[redacted]." (see section B2.9.9.2). However, the results of the ITC analyses (summarised in 3.4.2) suggest for some outcomes (e.g. number of patients on dialysis at endpoint in non-transplant patients, change in CKD stage in transplant patients), ravulizumab may be [redacted] than eculizumab. Whether these potential differences are reflective of genuine differences in effectiveness or residual confounding is highly uncertain:

1) The company's claim that there were no statistically significant differences between treatments doesn't accurately reflect the outcome data. For example, table 22 of the CS shows [redacted]

2) Failure to meet the threshold for statistical significance does not necessarily imply the treatments are of similar effectiveness since sample sizes were small for all populations in the ITC analyses. Although formal power calculations are needed to assess the required sample size for non-inferiority analyses in aHUS patients, it is likely there were insufficient sample sizes for all three populations in the ITC analyses ([redacted]). For example, the non-inferiority trial comparing eculizumab and ravulizumab in patients with PNH included a far larger sample size (195 patients).

   Therefore, where differences were not statistically significant, this may just reflect that sample sizes were of insufficient magnitude to detect important differences. There were several differences between groups approaching statistical significance. For example, in non-transplant patients, data on proportion of patients on dialysis at endpoint (ravulizumab [redacted] vs eculizumab [redacted]), and LDH, U/L (ravulizumab [redacted] vs eculizumab [redacted]), favoured eculizumab. Given limitations in sample size, genuine differences cannot be ruled out.

3) The CS stated that there were [redacted] between treatments. However, clinical advisers to the ERG judged this highly uncertain based on the data presented by the company as the sample sizes in trials were not large enough to rule out a clinically significant difference.

4) Although, there is evidence of non-inferiority between ravulizumab and eculizumab in PNH patients, clinical advice to the ERG concluded that extrapolation of these findings to aHUS patients is highly uncertain as they are different disorders.

3.4.3 Comparing safety data in ravulizumab and eculizumab

The company's response to question A15 of the PFCs provided naïve comparisons of safety data on ravulizumab and eculizumab (see table 5 of the company's response to question A15 of the PFC for full details).

The company argued that the safety data appeared similar across treatments. For example, all patients reported experiencing an adverse event (with the exception of aHUS-C10-003 where 20/22 (91%) reported any adverse events for eculizumab). There were a similar proportion of treatment-related adverse events in ravulizumab (ALXN1210-aHUS-311: 20/58 (34.5%), ALXN1210-aHUS-312 (Cohort 1): [redacted]) and eculizumab (aHUS-C08-002: 12/17 (71%), aHUS-C10-003: 9/22 (41%), aHUS-C10-004: [redacted]trials. Additionally, there were a similar number of serious adverse events in ravulizumab (ALXN1210-aHUS-311: 33/58 (56.9%), ALXN1210-aHUS-312 (Cohort 1): [redacted]) and eculizumab (aHUS-C08-002: [redacted]aHUS-C10-003: 13/22 (59%), aHUS-C10-004: 18/41 (44%)) trials.

In response to points for clarification, the company presented safety results for eculizumab from the aHUS global registry for 535 adult and 330 paediatric patients over 5 years.[19] Results are summarised in the company response to points for clarification document, Table 5. Rates of serious infection were 8.6% in adults and 9.7% in children, and deaths due to AE (all infections) were 1.5% in adults and 0.6% in children. Although this data is based on a significantly larger sample size than the trial evidence, comparability with eculizumab and ravulizumab trial evidence is limited by the observational nature of the data and significantly different follow-up durations.

3.4.3.1 Points for Critique

Given important differences between populations included in the ravulizumab and eculizumab trials, these findings are subject to even further uncertainty than the ITC analyses since the company did not attempt to match baseline population characteristics for safety data.

In addition, limitations in reporting of data made it difficult to draw comparison between treatments. For example, the severity of adverse events were graded differently in the ravulizumab and eculizumab trials.

Although results from trial 301 (PNH naïve) found that the safety of razulizumab is non-inferior to that of eculizumab, due to clinically relevant differences between PNH and aHUS populations, the applicability of these results to the decision problem is uncertain.

Although the assumption that ravulizumab and eculizumab have similar safety profiles is clinically plausible, there is insufficient data to confirm this.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG verified the company's ITC methods and code. No additional analyses were carried out.

3.6 Conclusions of the clinical effectiveness section

Due to their biological homology and similar mechanism of action, it is clinically plausible that ravulizumab and eculizumab have equivalent efficacy and safety in aHUS patients. However, the limited data means there is insufficient evidence to support this assumption.

The lack of randomised evidence for ravulizumab and eculizumab in aHUS patients, clinically relevant differences between the ravuzliumab and eculizumab trial populations and small sample sizes mean that indirect comparisons between the two treatments are at high risk of confounding and highly uncertain. ITC analyses did not include presence of pathogenic variants, despite substantial differences between treatments, as a factor to balance characteristics across groups. Results also show differences in effectiveness between treatments cannot be ruled out. However, due to multiple and potentially conflicting sources of confounding, the likely direction and magnitude of bias in the indirect comparisons are highly uncertain.

The generalisability of the ravulizumab trial population to the NHS is significantly limited. All of the ravulizumab adult trial population evidence and most of the paediatric evidence includes first-line/complement-therapy naïve patients. This differs from clinical practice, where for clinical reasons, it is expected that nearly all eligible patients would receive ravulizumab as second-line treatment following response to eculizumab therapy. In addition, the low prevalence of pathogenic variants in the ravulizumab trial population means that a potentially significant number of patients did not have aHUS. Therefore, most of the trial evidence is not representative of the population who would receive ravulizumab in NHS practice.

Due to limited follow-up, the long-term safety and efficacy of ravulizumab is uncertain. The ERG is concerned that the trial Extension Period duration is dependent on registration or approval (in accordance with country-specific regulations) of ravulizumab rather than for appropriate clinical reasons, and may therefore be insufficient to inform long-term efficacy and safety outcomes. The company did not provide further details and it is not clear how the approval of ravulizumab in the UK

(or abroad) may affect the duration of follow-up of trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

Disease recurrence following response to treatment was not captured in the ravulizumab trial evidence. Although the frequency of complement-therapy infusions is lower with ravulizumab compared with eculizumab, there is insufficient evidence to show that ravulizumab use translates into safety and quality of life benefits. In their clarification response, the company referred to a US based qualitative study of ten adult patients and three carers of paediatric patients who had switched to ravulizumab (from eculizumab) 4 to 10 months before study participation.[31] All respondents in the Global Action research study considered the longer infusion intervals as a key benefit of ravulizumab treatment. Although these results are encouraging, they are based on a very small sample size and these views may not be representative of UK patients.

Additional long-term ravulizumab efficacy and safety evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS is needed, including robust monitoring of disease recurrence, and treatment discontinuation and reinitiation.

Randomised evidence of ravulizumab versus eculizumab in aHUS patients would help clarify whether the assumption of equal efficacy and effectiveness is justified. However, the ERG acknowledges that given the ultra-rare nature of the disease, this evidence may never become available. Where possible, establishing non-inferiority between the treatments in a trial programme for aHUS may be required.

Additional long-term ravulizumab efficacy and safety evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS is also needed, including robust monitoring of disease recurrence, and treatment discontinuation and reinitiation. Once the SETS study [2] reports, a similar study could be designed that would seek to evaluate whether patients who relapse following disease relapse and treatment re-initiation can safely be withdrawn from treatment for a second or further time. Given the lack of evidence for alternative dosing of ravulizumab and eculizumab, studies evaluating a more flexible approach to dosing and infusion frequency, notably in the paediatric and adolescent population (<18 years), may be warranted. Evidence of quality of life benefits and patient preferences associated with switching to ravulizumab relevant to the NHS is required.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company's methods for reviewing the cost-effectiveness literature are outlined in Appendix G of the CS (pages 80-84). The CS included a combined search to identify economic evaluations, health-related quality of life studies, and cost and resource use studies in patients with aHUS. The company identified seven studies reporting only costs or HRQoL and two cost-effectiveness studies evaluating the use of eculizumab for aHUS against Standard of Care (summarised in Table 25 of the CS). Of the two cost-effectiveness studies, only one was conducted in the UK and was relevant to this appraisal. This study, which was the ERG's critique of eculizumab for treating aHUS as part of the NICE Appraisal of eculizumab (HST1), described a state-transition model with five mutually exclusive health states reflecting kidney function. The company used the ERG's critique as the basis for the development of the decision model submitted in this appraisal.

Points for critique

The ERG is satisfied with the company's review of the cost-effectiveness evidence (see Table 24 in Appendix B for a detailed appraisal of the company's searches for economic evidence). The searches are expected to have identified relevant cost-effectiveness studies on the treatment of aHUS. Given the rare nature of aHUS, it is not surprising that HST1 is the only study that matches the decision-making context of this appraisal (UK NHS and Personal Social Services perspective); hence the ERG agrees with the company's use of HST1 as a starting point to inform their submission.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

The company submitted a state-transition model that analysed adult and child populations separately and presented overall cost-effectiveness results weighted based on the proportion of adults ([redacted]) versus children ([redacted]currently treated in clinical practice. The company assumed equal efficacy and effectiveness between ravulizumab and eculizumab and, as a result, their base case corresponds to a cost-minimisation analysis. Differential efficacy in terms of CKD stage was assumed by the company in a sensitivity analysis that was based on the ITC analysis, and the results are presented under the company's 'worst-case scenario'.

4.2.1 NICE reference case checklist

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	The CS is appropriate.

Perspective on costs	NHS and PSS.	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	The company assumed in their base case that eculizumab and ravulizumab are equally efficacious and conducted a cost-minimisation analysis. Fully incremental analysis, assuming differential efficacy, is presented by the company in their `worst-case scenario' analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The CS is appropriate. Adult patients enter the model at an average age of 38.3 years old, whilst children enter at the average age of 5.8 years old. A maximum age of 100 years is assumed.
Synthesis of evidence on health effects	Based on systematic review.	The CS is appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company compares ravulizumab and eculizumab in terms of HRQoL only in their `worse-case scenario' analysis. This scenario is using EQ-5D-3L data. Children are assumed to have the same utility values as the adult population. The company applies a HRQoL increment, derived in a discrete choice experiment, to patients receiving ravulizumab to reflect the reduced frequency of infusions.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	EQ-5D-3L data were directly obtained from patients in the ravulizumab and eculizumab studies that enrolled adults.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	The CS is appropriate. Although, it should be noted that only 5/56 patients in ALXN1210-aHUS-311 study and 2/28 patients in ALXN1210-aHUS-312 study were from the UK.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	The CS is appropriate.

EQ-5D, standardised instrument for use as a measure of health outcome. HRQOL, health-related quality of life; PSS, personal social services; QALYs, quality-adjusted life years;

4.2.2 Model structure

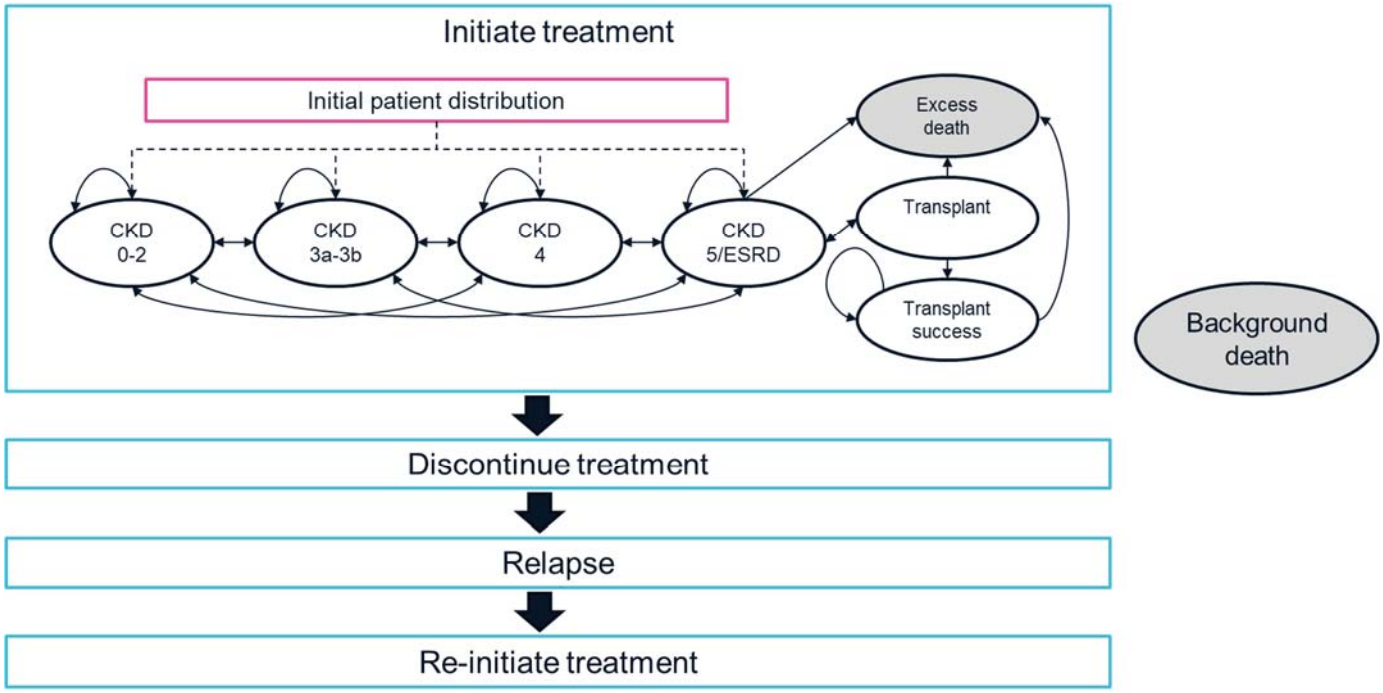
The company submitted a state-transition Markov model that simulates the long-term outcomes of aHUS patients over their lifetime. Patients receive either ravulizumab or eculizumab and no other treatment option is considered. The model uses a 14-day cycle length, without a half-cycle correction. The company justified their model structure based on consistency with the previous economic model submitted for HST1, which was considered representative of the aHUS pathway [3].

In HST1, the committee highlighted that the company's model assumed that patients would receive lifelong treatment with eculizumab, although the evidence on the optimal treatment duration was unclear [32]. Since then, studies have been investigating the potential for treatment discontinuation [7], and lifetime treatment will not necessarily be considered standard practice in the UK in the future. To accommodate the feedback received in the previous appraisal and recent changes to clinical practice in the UK, the company expanded the model submitted in HST1 to explicitly account for treatment discontinuation. As a result, the model developed for this appraisal included four mutually exclusive health states around treatment discontinuation: (1) Initiate treatment, (2) Discontinue treatment, (3) Relapse, and (4) Re-initiate treatment. Within each health state, there are eight sub-health states reflecting aHUS progression on renal outcomes: CKD Stages 0–2, 3a–3b, 4, 5/ESRD, transplant, transplant success, excess death, and background death. The transplant health state is a tunnel state that lasts for 1 model cycle only, after which if the transplantation is successful, patients transition to `transplant success', whilst if the transplantation failed they either move back to `CKD 5/ESRD' or die due to the excess death incurred in the process.

Transitions were allowed between any two CKD health states. To calculate transition probabilities the company fitted ordinal probit models (a form of regression analysis that is used to estimate relationships between an ordinal dependent variable and a set of independent variables) that treat CKD stage as the ordered categorical dependent variable. The independent variables included time and a lag variable describing a patient's CKD stage at the previous time-period (see Appendix P in the CS Document B for further details). The company used data from all available ravulizumab and eculizumab aHUS studies; however, only evidence from patients included in the FAS with complete data were included. Analyses were restricted to the first 52 weeks and to 5.5 years for the ravulizumab and the eculizumab studies respectively. In the company's base case, trial outcomes were pooled irrespective of treatment. However, in the company's main ITC analysis ('worst case scenario'), the same cut-off was applied to both ravulizumab and eculizumab, and transition probabilities were assumed to be time-dependent only during the first year and constant beyond that. The company presents further scenario analyses using a 1 year cut-off for ravulizumab and a 5.5 years cut-off for

eculizumab studies in Table 51 of the Appendix to Document B (page 130). The initial patient distribution across the sub-health states was derived using evidence from all the existing studies and was conditional on the population under consideration (i.e. adults or children). A schematic representation of the model is provided in Figure 4**Error! Reference source not found.**. The company cites feedback from clinicians to justify that the adapted model structure is appropriate.

Figure 4: Economic model diagram.



Key: aHUS, atypical haemolytic uremic syndrome; CEA, cost-effectiveness analysis; CKD, chronic kidney disease; ESRD, end-stage renal disease.
Figure adapted from CS Document B, Figure 16).

Points for critique

The economic model is largely consistent with the model submitted in HST1. However, the company reflected on the feedback received by the ERG and the committee during HST1, and made the following adaptations in this submission:

- The model was modified to consider both adults and children separately to appropriately calculate treatment dosages based on age and weight distributions, and subsequently weight the results of the two populations to produce the overall cost-effectiveness results.
- The model was adapted to reflect recent developments in UK practice and does not model lifelong treatment. Instead, it assumes that treatment may be discontinued once, and reinitiated in those patients whose disease relapses.
- The model was adapted to apply time-dependent transition probabilities (for the first year) amongst CKD health states in the ITC analysis. These were based on an ordered probit model.
- The derivation of the transition probabilities is based on a multi-stage modelling approach.

The ERG notes that the company's model makes the following key assumptions about the model's structure and key drivers of the transitions between health states:

Transitions

- ravulizumab and eculizumab patients can improve or worsen in terms of CKD stage.
- Transition probabilities are time-dependent during the first year but remain constant beyond that.

Treatment discontinuation

- Patients may discontinue treatment due to four reasons: misdiagnosis, no renal response, adequate renal response, general reasons including AEs and patient preferences.
- Patients can discontinue treatment only once in the model.
- General discontinuation rates do not differ between ravulizumab and eculizumab.
- Patients who discontinue due to adequate renal response, do so only at 6 months after treatment initiation, which is the minimum treatment duration for ravulizumab and in line with the minimum treatment duration within the SETS protocol. In other words, it is assumed that all the patients who achieve renal recovery do so by six months.

Disease relapse

- Patients face a constant risk of relapse throughout their treatment discontinuation period.

Treatment re-initiation

- All patients who relapse after treatment discontinuation, re-initiate treatment (irrespective of whether they had discontinued treatment for no renal response, renal response or general reasons) and remain on treatment for the remainder of their lifetime

Populations

- Adults and children are modelled separately, and their results are subsequently weighted based on the proportion of adults ([redacted]) and children ([redacted] treated in clinical practice.

The ERG considers the model structure to be generally appropriate. A minor point which was raised by the ERG's clinical advisors is that CKD stage is generally non-reversible, unless a patient receives transplant, and hence patients' CKD stage is not expected to improve but only deteriorate or remain stable. Given that the model aims to reflect renal function which retains the potential to improve, the health states could have been better defined in terms of Acute Kidney Injury (AKI) instead of CKD. This labelling would not affect the model structure, which would remain largely unchanged.

4.2.3 Treatment discontinuation, relapse and re-initiation

4.2.3.1 Treatment discontinuation

The company's model captures four reasons for treatment discontinuation: (1) misdiagnosis, (2) general discontinuation due to AEs or patient choice, (3) no renal response, and (4) adequate renal response. The company's modelling approach to the various reasons for discontinuation is detailed in Section B.3.3.1. (page 117 of Document B).

For misdiagnosis, the company adopts a simplified approach that takes account of the fact that around 17% of patients are misdiagnosed and discontinue treatment during the first month based on NRCTC reports. The company uplifts the costs of the first month in the model by 20% for both ravulizumab and eculizumab. For general discontinuation due to AEs or patient choice, the company fits parametric survival curves to the pooled eculizumab and ravulizumab trial data assuming that general discontinuation rates would not differ between eculizumab and ravulizumab. Parametric models were fitted separately for adults without a prior transplant, adults with prior transplant, and children. Model choice was primarily informed by the non-transplant data as more information was available for that subgroup. All parametric models were shown to fit similarly in terms of AIC/BIC and differences in their predictions were observed primarily in the extrapolation period. The company chose an exponential model for their base case analysis because the curve sat between the lower and upper predicted curves and assumed a constant rate of discontinuation over time. The company presented results of scenario analyses using alternative parametric models, which were demonstrated to have minimal impact on the cost-effectiveness of ravulizumab.

For no renal response, the model assumes that the proportion of patients who do not respond to treatment, and therefore discontinue, is 23% based on NRCTC reports.[5, 33, 34] Although the same proportion of patients is assumed to discontinue due to no renal response for both ravulizumab and eculizumab, the time point for discontinuation differs between the two treatments. Current clinical practice discontinues patients on eculizumab with no renal response after 3–4 months. However, to align with the minimum treatment duration for ravulizumab, outlined in the Summary of Product Characteristics, the company assumes that ravulizumab patients without renal response discontinue treatment after 6 months[35], whilst eculizumab patients discontinue after 3.5 months based on current practice.Finally, the company did not include discontinuation due to adequate renal recovery in their base-case analysis, but it was included as a scenario analysis. The company's justification for not including it in the base case is because of the lack of reliable data to inform the proportion of patients who would discontinue after having achieved stabilization, if not normalization, of renal function. Patients being considered for discontinuation for this reason are part of the SETS study, which is designed to assess the safety and impact of eculizumab withdrawal [2]. In the scenario analysis, the company explored the inclusion of discontinuation due to renal response by varying the proportion of

patients with adequate renal response. The scenario used a minimum treatment duration of 6 months for both ravulizumab and eculizumab based on the SETS protocol and assumed that either 65% of patients on treatment would discontinue based on preliminary assessment of SETS protocol, or 25% of patients would discontinue based on clinical opinion from a UK advisory board meeting.

4.2.3.2 Relapse and treatment re-initiation

The company's model assumes that patients who discontinue treatment for any cause except misdiagnosis and their disease subsequently relapses are eligible for treatment re-initiation. Specifically, in the base-case, the model assumes that 42.3% of adults and 50% of children who discontinued treatment will relapse and restart treatment at 3.56 and 3.99 years respectively, and that the corresponding probability of relapse is constant throughout the discontinuation period. These estimates are based on evidence obtained from UK patients in the aHUS registry, who were treated with eculizumab [37] and are consistent in the company's view with the long-term evidence from C11-003 study, whereby 50% of patients relapsed and resumed eculizumab treatment over a period of 5.25-5.45 years[38]. Crucially, once patients re-initiate treatment, they are not permitted to discontinue again and are assumed to remain on treatment for the remainder of their lifetime.

Points for critique

As noted by the company, clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard. Therefore, the ERG considers it important to model treatment discontinuation and welcomes the company's attempt to incorporate discontinuation in their analyses. There are several arguments against lifelong treatment. First, there is not adequate evidence to support lifelong treatment in every aHUS patient; instead, there is a growing literature suggesting that aHUS patients who discontinue treatment may not relapse, and that even when they do relapse, treatment is rapidly re-initiated and patients could recover their baseline renal function. For instance, in Fakhouri et al., 2017 all relapsing patients reinitiated treatment and recovered their baseline renal function[39]. Second, complement-inhibitor treatment is associated with potential adverse events such as susceptibility to infections and especially meningococcal disease [40, 41]. Third, recent evidence suggests that eculizumab may cause hepatotoxicity, leading to liver enzyme abnormalities and potentially drug-induced liver injury [42, 43]. Fourth, eculizumab, in particular, is associated with high administration burden and frequent infusions impact on patients Health Related Quality of Life (HRQoL). Fifth, lifelong treatment may increase the risk of immune-mediated drug reactions which may ultimately lead to the development of neutralising anti-drug antibodies [44]. Finally, complement-inhibitor treatment is associated with very high treatment costs; indicatively, the cost of ravulizumab for the first year is estimated to be around [redacted].

In terms of deriving estimates for the general discontinuation rate for eculizumab and ravulizumab, the ERG and its clinical advisors support the company's approach that pools the trial evidence for

eculizumab and ravulizumab. The ERG is also satisfied that the model incorporates all potential reasons for discontinuation of treatment. However, the ERG has a number of concerns in relation to the appropriateness of the assumptions and evidence used to inform the overall discontinuation rate:

1. Discontinuation due to adequate renal response is not included in the company's base case analysis

In the CS (page 110; Document B) the company states that *"Clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard for all patients."*. However, the company did not include discontinuation due to renal response in their base-case and justified their approach based on the lack of adequate data to inform the proportion of patients who would be eligible for treatment discontinuation due to renal recovery. The ERG acknowledges that the existing evidence base on discontinuation is limited to case-reports [6] and that the SETS study [45] which is designed to shed more light on this question has not yet reported results. Yet, the ERG considers that the company's base case should aim to reflect the likely changes in clinical practice.

Furthermore, the company's base-case assumes that adults and children who discontinue treatment are subject to a constant 0.59% and 0.66% probability of relapse and re-initiation of treatment in each two-weekly model cycle, respectively. This implies that around 50% of patients who discontinue treatment will re-initiate treatment within five years. The ERG believes that if discontinuation due to adequate renal response is excluded (as per the company's base case), it may not be realistic to assume that such a high proportion of patients would re-initiate treatment. This is because it is likely that the preponderance of patients who re-initiate treatment do so because they have evidence that complement-inhibitor treatment adequately controls their disease. As a result, the ERG deems that it is unlikely that 50% of patients who discontinued treatment due to reasons other than adequate renal response would re-initiate treatment within five years, and therefore it is unrealistic to exclude renal response from the base-case analysis.

item 1. Discontinuation due to adequate renal response is not included in the company's base-case analysis

2. Rate of relapse and re-initiation of treatment may be overestimated in the company's base-case analysis

The ERG highlights that the company's base-case analysis assumes that among adults and children who discontinue treatment, 42.3% and 50.0%, will relapse within 3.56 years and 3.99 years, respectively, and will require treatment re-initiation. The company derived these estimates from UK patients included in the aHUS registry in which 11/26 adult patients and 7/14 children relapsed and

re-initiated eculizumab treatment [37]. Similar estimates were also reported by Menne et al. (2019) for patients who relapsed and resumed eculizumab treatment [38].

The CS also indicates that these estimates are in line with TMA recurrence after discontinuation of eculizumab from other published studies ranging from 20 to 67%. The ERG notes that these estimates are based on 8 case-series studies which are shown in Table 13. All studies, except one, report a proportion of patients who discontinued treatment that is equal or lower than 31%. A higher proportion is only reported by the authors' case-reports of Macia et al., 2017 but it pertains to a very low number of patients (n = 6). Interestingly, the same study's summary of clinical series reports a much lower proportion of relapse of 20%. Furthermore, an analysis of the evidence from the global aHUS registry that included the global number of patients with aHUS by August 2014 estimated a relapse rate of 10% for adults and 25% for children [46]. Also, a recent retrospective review analysed 194 patients who discontinued eculizumab and found that 56 patients (i.e. 28.8%) relapsed. This review highlighted that there is substantial heterogeneity across genetic mutations with patients not having any genetic mutations relapsing only rarely, whilst patients with 'high-risk' mutations relapsing in more than 80% of cases [47]. Similarly, a recent update of the French STOPECU study found that out of the 55 patients who discontinued treatment, 13 (23%) relapsed and re-initiated and concluded that eculizumab can be safely discontinued once complement genetics are taken into consideration [48].

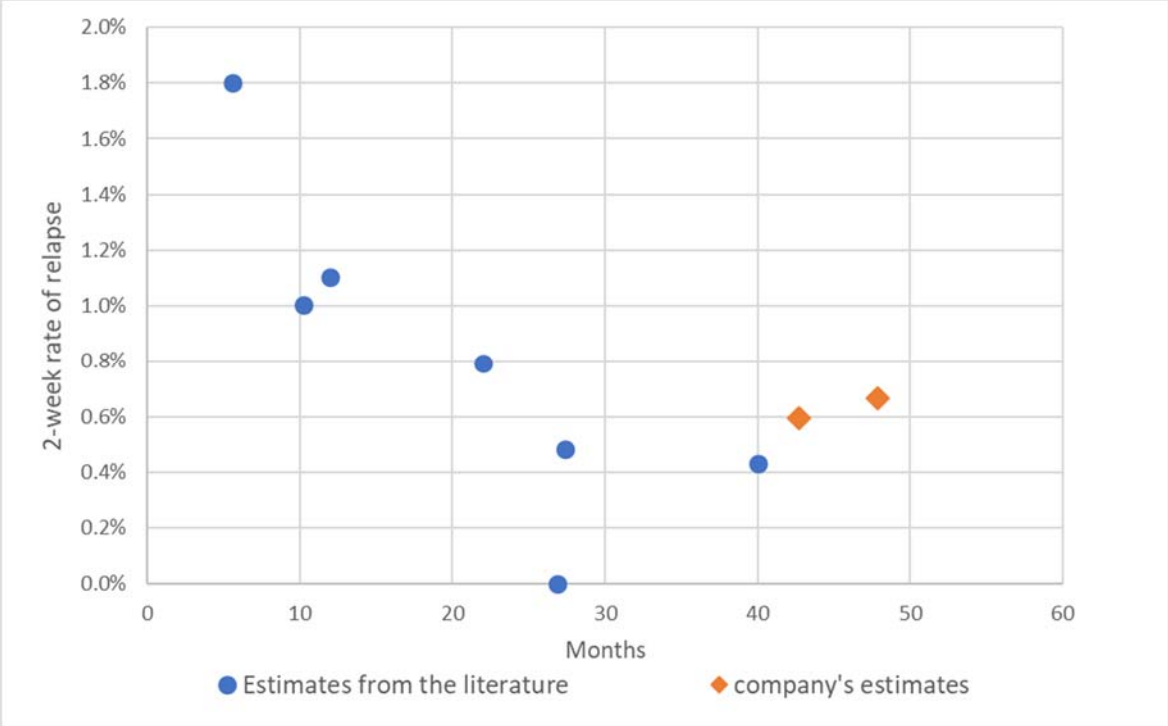
Table 13: Studies in which patients discontinued eculizumab treatment.

Study	Number of patients who relapsed / Number of patients who discontinued (%)	Mean follow-up (months)	2-week relapse rate
Company's base case (adults)	11/26 (42.3%)	42.72	0.59%
Company's base case (children)	7/14 (50.0%)	47.88	0.67%
Ardissino 2014 and Ardissino et al., 2015[44, 49]	5/16 (31%)	40	0.43%
Sheerin, 2016[50]	3/12 (25%)	12	1.10%
Fakhouri, 2017 [39]	12/38 (31%)	22	0.79%
Merrill., 2017 [51]	3/15 (20%)	10.2	1.01%
Macia, 2017[52] - summary of authors' case-reports	4/6 (67%)	NA	NA
Wijnsma, 2018[53]	5/20 (25%)	27.4	0.48%
Ardissino, 2018 [54]	0/9 (0%)	26.9	0.00%
Macia, 2017 [52]- summary of clinical series	12/61 (20%)	5.6	1.80%

Adapted from Wijnsma et al., 2018 [6]

The ERG notes that when the mean follow-up period of each study is taken into account, the company's calculated 2-week relapse rate is not too dissimilar from those reported in the literature. However, comparing the 2-week relapse rates from a set of studies with considerably different follow-up periods makes the implicit assumption that relapse rates are constant through time (which will be discussed later). Though, the current evidence from the literature suggest that relapse rates are not constant; instead, they are higher shortly after treatment discontinuation and significantly lower after around one year of sustained disease control [6, 20]. Figure 5 compares 2-week relapse rate estimates between the company's base case and the studies reported in Table 13. The figure clearly shows that the longer a study's follow up, the lower its reported relapse rate, and the company's estimates seem to deviate from the overall trend and therefore potentially overestimates the expected 2-weeks relapse rate.

Figure 5: Two-week relapse rates according to mean follow-up periods in the company's model and the available studies in the literature.



The ERG sought further advice from its clinical advisors on the potential reasons for the observed discrepancy between the UK and global estimates of relapse and re-initiation of treatment. The clinicians suggested that non-UK countries may follow a more `sensitive' approach and initially treat more patients who end up not having aHUS. As a result, a lower proportion of patients who discontinue stand to benefit from treatment re-initiation in non-UK countries compared to the UK. The clinicians could not identify any other reasons to expect higher relapse rates in the UK.

In response to the ERG's points for clarification document, question B2, the company highlighted a recent study (accepted but publication pending) that analysed patient outcomes after treatment discontinuation using the global aHUS registry. Importantly, patients who had an alternative diagnosis as a reason for discontinuation were excluded from this analysis so the aforementioned justification for differential relapse rates would not apply [55]. Out of the 151 patients who discontinued treatment and had a median follow-up of 2.3 years, 30 (i.e. 19.9%) restarted treatment, implying a probability of relapse of 0.37% within each two-week model cycle [56]. This estimate is based on considerably more patients (i.e. 151 patients who discontinued eculizumab globally) than the company's estimate which is based on only 40 UK patients and is better aligned with the estimates provided in the evolving literature around this topic. The ERG notes that the company's sensitivity analyses varied the 2-week probability of relapse in a range of 0.48% – 0.71% for adults and 0.54% - 0.8% for children (see tornado plot in Figure 23 of the CS Document B; page 151); hence, no results have been presented for relapse rates similar to those suggested by the updated analyses by Ariceta et al., 2020. The ERG considers the estimate of 19.9% (that is equivalent to a 2-week probability of relapse of 0.37%) to be a more accurate reflection of the relapse rates for patients who discontinue treatment, that is more aligned with several of the estimates from studies reported in Table 13. In the absence of a separate estimate of relapse rate for adults and children, the ERG considers it appropriate to use the same relapse rate as an approximation for both age groups.

item 2. The rate of relapse following treatment discontinuation may be overestimated in the company's base-case analysis

3. Rate of relapse is assumed to be constant through time

In the company's model, patients who discontinue treatment are subject to a constant relapse rate based on evidence from UK patients in the aHUS registry over 3.56 years for adults and 3.99 years for children. The company derives the estimate of the probability of relapse over the follow-up period by dividing the total number of patients who relapsed over the follow-up period by the total number of patients who discontinued treatment with eculizumab. The corresponding two-week relapse probabilities are then applied in each model cycle over the duration of the model's time horizon. Therefore, the company assumes that the same relapse rate that applied during the first 3.56 years for adults (or 3.99 years for children) would apply constantly in the model. As a result, within 10 years from discontinuing treatment, around 80% of adults (86% of children) have relapsed and started lifelong treatment.

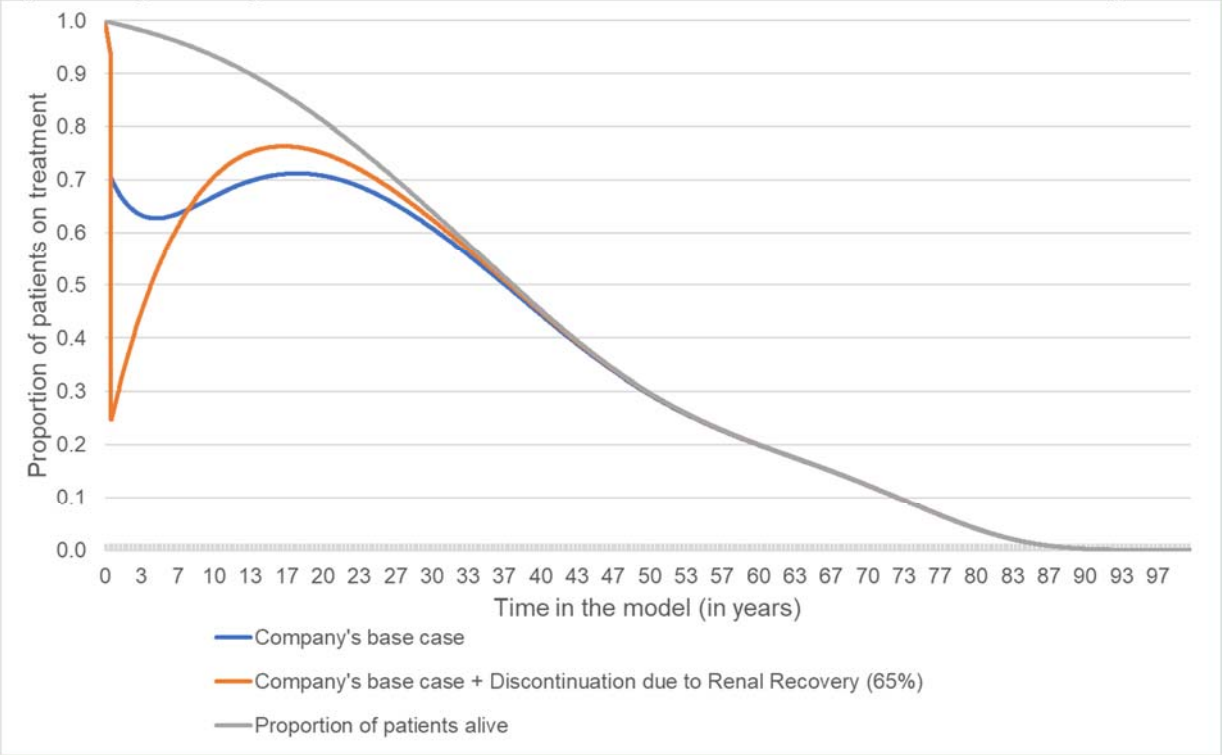
The ERG notes that the company's method of estimating the relapse rate by just dividing the number of patients who relapsed over a specific time period may not be considered appropriate because it

cannot appropriately account for censoring. Therefore, a survival modelling approach based on UK patients in the aHUS registry would have been more suitable.

Importantly, the company's assumption of constant relapse rate is not supported by the existing literature. Indicatively, Wijnsma et al., 2019 report that across nine case-report studies (shown in Table 13), the median (range) time to relapse was 3 months (1–29.5 months). The ERG's clinical advisors also indicated that the risk of relapse is higher shortly after treatment discontinuation and is considerably reduced in later years, conditional on sustained remission. This is also in agreement with reports from the pre-eculizumab era, which indicated that 57–82% of relapses occurred during the first year of follow-up and that risk decreased from >80% to around 25% in almost all aHUS patients after the first year [20].

The ERG highlights that the company's assumption of a constant relapse rate based on a short follow-up of around 3.5 – 4 years is likely to overestimate the proportion of patients who relapse over the model's time horizon. This is illustrated in Figure 6 which shows the proportion of patients who are on treatment over time across a number of scenarios. The grey line corresponds to a no discontinuation scenario, where patients discontinue treatment only due to mortality effects (this is just shown as a reference to demonstrate the impact of discontinuation in the model), the blue line corresponds to the company's base-case assumption, where there is no discontinuation due to renal recovery (only reasons for discontinuation are no renal recovery and general causes), and the orange line corresponds to the scenario where 65% of patients who are still on treatment at 6 months discontinue due to adequate renal response (company's scenario analysis). Interestingly, although in the scenario analysis the proportion of patients on treatment initially falls sharply, it quickly recovers and surpasses that of the company's base case analysis at around 8 years. Indicatively, 70% of patients who discontinued treatment at 6 months in the scenario analysis have returned to lifelong treatment within 8.5 years. This is because the company's model assumes a 2-week probability of relapse rate of 0.59% (0.66% for children) that is equivalent to a 54% chance of relapse (58% for children) over 5 years and a 71% (75% for children) over 8 years. Consequently, the proportion of patients who discontinue treatment due to adequate renal response has little effect on the company's overall cost-effectiveness results because the majority of patients who discontinue get back on treatment relatively quickly and for their remaining lifetime.

Figure 6: Proportion of patients on treatment over time with and without discontinuation due to renal response



Graph obtained using the company's submitted economic model.

item 3. A constant relapse rate may overestimate the proportion of patients who relapse in the long-term

4. Second and subsequent treatment discontinuations

The company's approach assumes that once a patient discontinues treatment and their disease subsequently relapses, they will receive complement inhibitor therapy for the remainder of their lifetime. Therefore, the model allows patients to discontinue only once and does not provide sufficient flexibility to model multiple treatment discontinuations/re-initiations.

To evaluate the plausibility of this assumption, the ERG sought advice from clinical advisors. There was a consensus among clinical advisors that practice in aHUS is rapidly changing as the literature evolves around the use of complement-inhibitor treatments. It is likely that for the majority of patients practice will soon change from lifelong treatment and instead aHUS will be managed as a treatment/relapse disease, i.e. patients who relapse would receive a new treatment course until they subsequently discontinue again. The ERG acknowledges that the literature has not yet matured on this topic, and the clinicians' expectations may not necessarily be confirmed. However, the ERG notes that the probability of discontinuation and subsequent relapse, as well as the number of possible discontinuations/re-initiations, are important drivers of drug acquisition costs and hence cost-effectiveness of complement-inhibitor treatments. Indicatively, if we were to assume that patients

never discontinue treatment, the incremental costs of ravulizumab vs. eculizumab would amount to around [redacted]. In contrast, in the current version of the company's model that allows for only one discontinuation the incremental costs amount to around [redacted]. This means that the impact of the assumptions surrounding treatment discontinuation has a substantial effect on cost-effectiveness. The ERG expects that modelling additional discontinuations would lead to considerable further reductions in the incremental costs, albeit of a lower magnitude.

In response to ERG's points for clarification document, question B2, which requested a more flexible economic model that can accommodate multiple discontinuations, the company did not provide an updated model structure for two reasons: first, because there is very limited evidence from patients who discontinued treatment more than once, and therefore it is challenging to inform the relapse rates of subsequent discontinuations, as well as the criteria that would be met for a patient to discontinue for a second time; and second, because it deemed that "*Adding in another layer of treatment discontinuation would have added additional complexity to the structure, and based on little data and clinical backing, was considered unnecessary*."

The ERG agrees with the company that there is very limited evidence to inform an analysis of multiple discontinuations. However, the potential for complement-inhibitor treatments to be used `on-demand' has been discussed in the recent literature as potential future practice. Indicatively, Wijnsma et al., 2019 mentions that amongst 17 patients who relapsed and re-initiated eculizumab after an initial eculizumab discontinuation, 3 patients with pathogenetic mutations discontinued for a second time and no relapses had been reported [6]. The authors then clearly state that "*This suggests that even in a proportion of patients with disease recurrence, lifelong treatment is not necessary*". In their response to question B2, the company also indicated that in the long-term eculizumab study (C11-003), 21 patients restarted treatment after discontinuation and, of those, 6 discontinued treatment for a second time (for reasons other than end of study period).

The ERG notes that the company's simplified model structure that assumes lifelong treatment following a single treatment discontinuation is potentially overestimating the cost savings of using ravulizumab instead of eculizumab.

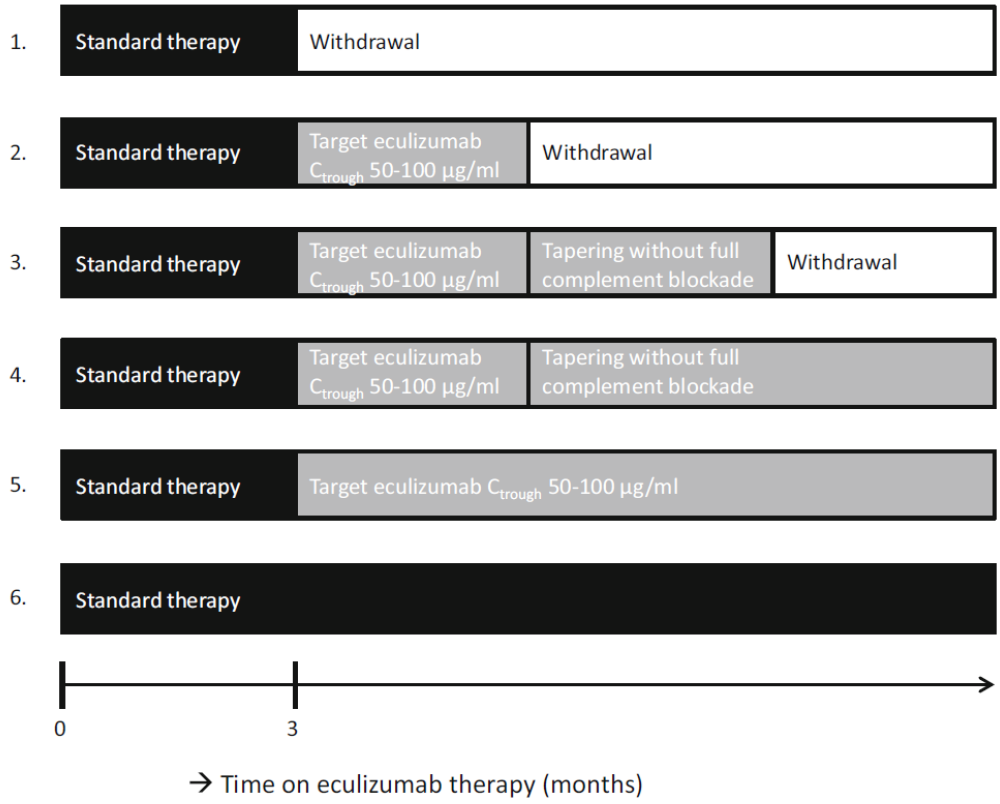
item 4. The company's approach to treatment discontinuation may overestimate incremental costs if more than one discontinuation is permitted in clinical practice.

5. Alternative treatment strategies

Finally, the ERG notes that following an initial treatment period, treatment discontinuation is not the only strategy. Instead, several restrictive treatment strategies have recently been described [6]. For

example, one option is to adapt the dosage of the complement-inhibitor to target trough levels of 50–100 µg ml−1 with complete blockade of the complement system. Another option includes tapering with incomplete complement blockade. Also, prolonging the period between eculizumab infusions has been attempted [53]. Other options include combinations of the above strategies with or without treatment withdrawal. A list of the potential restrictive treatment strategies is provided in Figure 7. The ERG acknowledges that there is very limited evidence on the effectiveness of each of the possible treatment strategies and therefore the best strategy is currently unknown. However, strategies 2-5 sit between the two extremes and may considerably avoid the disadvantages of prolonged treatment, whilst also achieving a reduced relapse rate compared to strategy 1 that is considered in the company's model. These restrictive strategies may therefore offer adequate disease control and play a role in facilitating a second or subsequent treatment discontinuation.

Figure 7: Possible treatment strategies for aHUS patients.



Adapted from [6].

item 5. The optimal treatment strategy for complement-inhibitor treatments is uncertain.

4.2.4 Population

The population considered by the decision problem is adults and children 10 kg or above with aHUS who are complement-inhibitor treatment-naïve or have received eculizumab for at least 3 months and have shown evidence of response to eculizumab. The company's model considers only treatment-

naïve patients due to the lack of data from patients who switched from eculizumab and assumes that ravulizumab would be equally efficacious in treatment-naïve and treatment-experienced patients.

In the company's model, the population corresponds to the pooled ravulizumab and eculizumab trial data after 'stabilised weights' were applied to balance the characteristics of the two groups (Section 3.4). A summary of the baseline characteristics of the adult and children populations is provided in Table 14. It should be noted that Table 14 is based only on patients who weighed more than 10kg. However, despite not being included in the licenced population, the company's base case-analysis includes the data of seven patients who weighed less than 10kg (three patients who received ravulizumab in ALXN1210 -aHUS-312 - 8.5 kg, 8.8 kg and 9.1 kg - and four patients who received eculizumab in C10-003 - 6.7 kg, 8.3 kg, 8.5 kg and 9.9 kg). The company justifies the inclusion of these patients in their base-case analysis based on the fact that their weight was close to 10 kg and that excluding them would decrease the sample size.

Table 14: Baseline characteristics by population

Patient demographic	**Adults**	**Children**	**Source**
Age, mean	[redacted]	[redacted]	311 312 C08-002 C10-003 C10-004
Percentage female	[redacted]	[redacted]	
Weight, mean (kg)	[redacted]	[redacted]	
Weight distribution (kg)			
≥ 10 to < 20	[redacted]	[redacted]	
≥ 20 to < 30	[redacted]	[redacted]	
≥ 30 to < 40	[redacted]	[redacted]	
≥ 40 to < 60	[redacted]	[redacted]	
≥ 60 to < 100	[redacted]	[redacted]	
≥ 100	[redacted]	[redacted]	
CKD stage distribution			
0–2	[redacted]	[redacted]	
3a–3b	[redacted]	[redacted]	
4	[redacted]	[redacted]	
5/ESRD	[redacted]	[redacted]	

Key: CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table adapted from CS Table 27.

Adult and children are analysed separately in the model using different sources of evidence to inform each analysis. Overall cost-effectiveness results for ravulizumab are then presented by weighting the two populations according to the current number of patients in each population treated for aHUS in the (NRCTC) in Newcastle upon Tyne i.e. [redacted] adult ([redacted]%) and [redacted] children ([redacted]%) patients.

Points for critique

As discussed in detail in Sections 3.2.1.2 and 3.2.2.2., the ERG considers there to be uncertainty in the generalisability of the patients included in the ravulizumab studies to patients who would be expected to be eligible for ravulizumab treatment in the UK.

An important characteristic of study ALXN1210-aHUS-311 was that four patients in the adult, non-transplantation, group died. However, the company's `worst-case scenario' analysis was based on an ITC that excluded the data pertaining to these four patients. The company justified this approach based on the fact that these patients presented in a critical condition, would be considered high-risk, and would *not* be treated with complement-inhibitor treatment in the UK. The ERG's clinical advisors shared this same opinion. Therefore, the ERG accepts the company's rationale and deems that the results of the analysis that excludes these patients is more likely to represent patients eligible for treatment in the UK. In response to the ERG's points for clarification document, question B3, the company provided an analysis of an extreme scenario where these deaths were included for ravulizumab and no deaths for eculizumab. The results of this scenario did not have a material impact on cost-effectiveness.

The ERG further notes that the patients included in the ravulizumab studies were primarily eculizumab-naïve. However, the ERG's clinical advisors indicated that it is likely that in the majority of cases ravulizumab would be used only after an initial period in which patients would receive eculizumab. Therefore, the question of whether ravulizumab is equally effective in eculizumab-naïve patients and in patients who switch after receiving eculizumab remains uncertain. The company supports the recommendation of ravulizumab for eculizumab-experienced patients based on a subgroup of n=10 children included in ALXN1210-aHUS-312 who switched after at least 90 days of treatment with eculizumab and remaining clinically stable. These patients maintained disease control after switching to ravulizumab and continued to have evidence of complement blockade. The company also provides evidence from a Phase III trial enrolling n=197 PNH patients (ALXN1210-PNH-302). After at least six months receiving eculizumab and being clinically stable, these patients switched to ravulizumab and maintained disease control with evidence of complement blockade.

item 6. The generalisability of the populations included in the ravulizumab trials to UK clinical practice is uncertain.

4.2.5 Intervention and comparator

As per the decision problem, the intervention considered in the model is ravulizumab, whilst the comparator is eculizumab. This differs from the decision problem in HST1 which considered eculizumab as the intervention and supportive care as the comparator. Both ravulizumab and eculizumab bind to complement protein C5 inhibiting terminal complement-mediated inflammation

and preventing immune activation and haemolysis. Although both treatments function through the same mechanism, ravulizumab binds to its substrate with higher affinity and achieves a quadruple half-life; thus, requiring less frequent administration.

Treatment with ravulizumab starts with a loading dosage, followed by the first maintenance dose 2 weeks later and subsequent maintenance dosages every 8 weeks. In contrast, eculizumab treatment requires weekly infusions for an initial period of 4 weeks, followed by the first maintenance dosage on week 5 and further maintenance dosages every 2 weeks. The dosing schedules for the ravulizumab and eculizumab according to the patient's weight are provided in Table 15.

Table 15: Dosing schedules of ravulizumab and eculizumab for adults and children.

Treatment	Population	Body weight (kg)	Dose	Source
Ravulizumab	Adults	≥ 40 to < 60 ≥ 60 to < 100 ≥ 100	2,400 mg followed by 3,000 mg every 8 weeks 2,700 mg followed by 3,300 mg every 8 weeks 3,000 mg followed by 3,600 mg every 8 weeks	SmPC[35]
	Children[a]	≥ 10 to < 20 ≥ 20 to < 30 ≥ 30 to < 40	600 mg followed by 600 mg every 4 weeks 900 mg followed by 2,100 mg every 8 weeks 1,200 mg followed by 2,700 mg every 8 weeks	
Eculizumab	Adults	NA	900 mg weekly for four doses and 1,200 mg for the fifth week followed by 1,200 mg every 2 weeks	SmPC[36]
	Children*	≥ 10 to < 20 ≥ 20 to < 30 ≥ 30 to < 40	600 mg weekly for one dose followed by 300 mg every 2 weeks 600 mg weekly for two doses followed by 600 mg every 2 weeks 600 mg weekly for two doses followed by 900 mg every 2 weeks	

Key: SmPC, summary of product characteristics; kg, kilograms; NA, not applicable.
Note: [a] Children over 40 kg have the same dosing schedule as adults.

Table adapted from CS Table 30.

Points for critique

The ERG considers the company's approach with respect to the intervention to be appropriate and consistent with the decision problem. The ERG notes that the company's model considers ravulizumab only for complement-inhibitor naïve patients. However, the ERG's clinical advisors indicated that in most cases they would expect ravulizumab would be used after an initial 3-month period when patients would receive eculizumab. As a result, the ERG considers it more representative

of UK clinical practice to model eculizumab and ravulizumab as a treatment sequence in the intervention arm with patients first receiving eculizumab for an initial period; however, the ERG acknowledges that the impact of modelling this treatment sequence on the cost-effectiveness results would be expected to be minor.

Regarding the comparator, the use of eculizumab (Soliris) is appropriate. Since the advent of eculizumab, which was a step change in the management of aHUS patients, practice has changed and best supportive case including plasma therapy is only rarely considered in some countries and under specific circumstances. However, the ERG notes that other treatments are expected to become available within the next few years. Specifically, an eculizumab biosimilar, ABP 959, is already being developed by Amgen. Studies have already demonstrated pharmacokinetics (PK) and pharmacodynamics (PD) bioequivalence, as well as similarity of ABP 959 to Soliris in terms of safety and immunogenicity profiles [57]. Currently, ABP 959 is at Phase III for PNH and Phase I for HUS [58]. Since the current patent for Soliris is expected to expire on November 2023 [1], it is not unlikely that eculizumab biosimilar treatments will be available for aHUS patients by then.

The ERG highlights that if an eculizumab biosimilar is offered at an adequate discount, then ravulizumab may not be cost saving anymore. Furthermore, if ravulizumab were to be approved, current practice would potentially switch from eculizumab to ravulizumab. Therefore, once the patent for Soliris expires and eculizumab biosimilars enter the market, it may be challenging for clinicians and patients to switch back to a treatment like eculizumab that has different pharmacokinetic properties and is associated with increased treatment administration burden compared to ravulizumab.

item 7. Eculizumab biosimilar treatment are likely to become available within the next five years.

4.2.6 Perspective, time horizon and discounting

The model adopts the NHS and Personal Social Services perspective. In the company's base-case, the model discounts costs and outcomes at 3.5%, in line with the NICE reference case, and adopts a lifetime time horizon. Sensitivity analyses using lower discount rates for costs, and shorter time horizons were considered but the company did not make a case for lower discount rates to be applied.

Points for critique

The ERG considers the company's approach to perspective, time horizon, and discounting to be appropriate. The ERG notes that in HST1 a discount rate of 1.5% was considered appropriate as eculizumab was likely to restore people to near full health and sustain it for over a long time-period compared to the alternative treatment, which was best supportive care. In contrast, in this appraisal the company compares ravulizumab against eculizumab and both treatments are likely to achieve similar

health benefits. Therefore, the company correctly opted for a 3.5% discount rate in their base-case analysis. The company explored higher and lower discount rates in scenario analyses which led to considerable changes in incremental costs. However, the ERG believes that the discount rate used in the company's base case is more appropriate and in line with NICE methods guide [59].

4.2.7 Treatment effectiveness and extrapolation

The company's base-case assumes that ravulizumab and eculizumab are equally efficacious. The company justifies their approach based on four main arguments:

1. The ITC analysis did not yield any statistically significant or clinically relevant differences (see Section 3.4.2.1.),

2. Eculizumab and ravulizumab share over 99% homology and function through the same mechanism of action,

3. Non-inferiority studies in PNH showed that ravulizumab is non-inferior to eculizumab [9, 60], and

4. The EMA has accepted that the two treatments have similar efficacy [17].

Based on these arguments the company adopts a cost-minimisation approach in their base-case analysis, where the transition probabilities in the model are assumed equivalent for both ravulizumab and eculizumab and the only difference between the two treatments is the time point for treatment discontinuation due to no renal response (6 months for ravulizumab and 3.5 months for eculizumab).

The company also presents a scenario analysis (termed 'worst-case scenario' in CS) where differential efficacy is assumed between ravulizumab and eculizumab. It should be noted that for this scenario the model does not apply a relative effect on the transition probabilities of the baseline treatment. This is because there is no direct relative effectiveness evidence from an RCT comparing ravulizumab and eculizumab, or evidence from studies comparing ravulizumab and eculizumab with a common comparator. Instead, the company applies transition probabilities for changes between CKD health states based on absolute effects observed in single-arm non-randomised eculizumab and ravulizumab trials. Therefore, the absolute effects of ravulizumab and eculizumab and their uncertainty are separately analysed and subsequently compared. This scenario is based on the ITC analysis which combined the two ravulizumab and the three eculizumab trials and used stabilised weights to balance the two treatment groups according to important patient characteristics (Section 3.4.1.). Importantly, the ITC results that were carried forward in the economic model excluded four adult patients who died during the study period because these patients presented in a critical condition and died from AEs that were considered unrelated to the study drug (see page 92 in the CS Document B). Finally, it

should also be noted that this scenario only captures differences in one outcome (i.e. CKD stage) and no other endpoints are considered in the model.

Points for critique

As discussed in detail in Section 3.4.2., there are a number of uncertainties associated with the company's approach to treatment efficacy and relative effectiveness. First, there are currently no direct head-to-head randomised studies of ravulizumab vs. eculizumab and the evidence base is limited to single-arm studies using ravulizumab or eculizumab. Although the ERG acknowledges that the ultra-rare nature of the disease prevents the production of randomised evidence, we highlight that any conclusions regarding the relative effectiveness of ravulizumab and eculizumab are prone to bias.

In the absence of comparative evidence, the company implements propensity score matching methods that balance the eculizumab and ravulizumab treatment groups according to a set of important observed patient characteristics. The ERG notes that this approach is reasonable; however, propensity scoring has the potential to produce unbiased estimates only when conditioned on the all relevant patient characteristics. When there are any unobserved important prognostic characteristics, the estimates may be biased. The company tried to alleviate this issue by seeking extensive clinical input to inform the characteristics but given that the scientific community has not reached a consensus on an exhaustive list of prognostic factors, it cannot be guaranteed that all important patient characteristics were included. For example, the company's ITC analysis did not match patients on their genetic mutations or the presence of anti-CHF antibodies, despite the fact that these parameters are known prognostic factors for aHUS [39, 53]. In response to ERG points for clarification, question A10, the company justified the exclusion of these factors based on the following reasons: these parameters were not raised by the clinicians in the company's clinical validation process; less than 70% of patients currently treated with eculizumab for aHUS have an identified genetic variant; and new genetic mutations have been identified and characterised recently, rendering the older evidence from eculizumab trials and the more recent evidence from ravulizumab trials incomparable.

The company justified the cost-minimisation (equal efficacy and effectiveness) approach adopted in their base-case based on the absence of any statistically significant differences between treatment groups for any outcomes after the application of propensity score methods, as well as other reasons detailed at the beginning of this section. The ERG notes that these analyses are based on a low number of patients (65 ravulizumab and 74 eculizumab patients) which were further split into three subgroups according to age and whether patients had received a transplant, and separate analyses were run within each subgroup. Therefore, any differences in outcomes between ravulizumab and eculizumab may not have been detected due to low statistical power.

The ERG also notes that there were differences in the way that ravulizumab and eculizumab studies defined a 'dialysis' patient. Specifically, in the ravulizumab studies this was defined as a dialysis within 5 days of a baseline/endpoint measure, whilst in eculizumab studies, this was within 7 days of a baseline/endpoint measure. The ERG sought input from clinical advisors who thought that this difference is unlikely to considerably affect results.

Finally, the company's analyses use the evidence reported in ravulizumab and eculizumab studies at 52 weeks and 5.5 years respectively, and project them through the patients' lifetime. The ERG notes that a period of 26 weeks is adequate to establish that ravulizumab and eculizumab are effective treatments for aHUS; however, given that in both the ravulizumab and the eculizumab studies patients experienced considerable improvements, it is uncertain whether the effect of treatment was stabilised within 26 weeks and whether the magnitude of the effect could differ in the long term.

item 8. It is uncertain whether ravulizumab and eculizumab can be considered equally efficacious.

4.2.8 Adverse events

The company's model does not account for AEs in their base-case or scenario analyses. The company justified this approach based on clinical feedback indicating that it is expected that the two treatments would have similar AEs profiles [61] and on a previous head-to-head assessment of ravulizumab and eculizumab for PNH that demonstrated similar safety profiles [9, 60]. A comparison of AEs across the ravulizumab and the eculizumab trials can be found in the CS (Appendix F of Document B; page 78).

Points for critique

As detailed in Section 3.4.3., the ERG considers there to be uncertainty with respect to the similarity of the AEs profiles of ravulizumab and eculizumab. However, in the absence of further evidence, the ERG considers the company's approach to exclude AEs from the economic model as appropriate.

4.2.9 Health related quality of life

Given that the company's base-case analysis considers ravulizumab and eculizumab to be equally efficacious and effective on all aspects of outcome, no differences in HRQoL were considered. However, in the company's `worse-case scenario', differential efficacy is assumed and HRQoL differences are included.

The company conducted a systematic review to identify HRQoL evidence for patients with aHUS (see CS Appendix H of Document B). Besides the ravulizumab trials, this systematic review identified only two studies reporting HRQoL for eculizumab [3, 62] (see Table 35 of the CS Document B). The company concluded that the HRQoL data in these studies were not well reported.

Given the lack of adequate information on HRQoL in the literature, the company preferred to use the HRQoL data reported in the eculizumab and ravulizumab studies. These studies directly collected EQ-5D-3L data; hence, no mapping algorithm was required. However, since HRQoL data were not routinely collected in these studies for children, they were assumed to have the same HRQoL as adults. The company notes that this assumption is consistent with previous appraisals [63, 64] but highlights that it is likely to underestimate the HRQoL of children because renal function generally improves more, haematologic outcomes are better, and levels of fatigue are lower in treated children relative to adults.

The company fitted mixed-effects models to estimate health-state specific utilities accounting for the repeated measurements within patients. Their selected model, shown in Table 34 of the CS (Document B; page 130), adjusts for baseline utility to account for the fact that the patients enrolled in the ravulizumab studies had lower utilities at baseline and hence showed greater improvement post-baseline than patients receiving eculizumab. Age-matched general population utilities were based on the Ara and Brazier algorithm [65]. To account for the fact that the trial-derived utilities for CKD Stage 0-2 were higher than the age-matched utility of the general population, a cap was introduced to ensure that it does not exceed the general population value for adults.

Patients receiving a transplant were assumed to experience the same utility as patients in the CKD5/ESRD state, whilst patients who had a successful transplant were assigned the average utility across CKD Stage states 0-4. A utility decrement of 0.1 was assumed to apply for patients who discontinued treatment and their disease subsequently relapsed, whilst a 5.5% utility reduction was explored in a scenario analysis. Once patients who relapsed reinitiated treatment, they were assumed to experience the same utility that they had before discontinuation. Finally, to account for the improved dosing schedule of ravulizumab and the need for less frequent infusions, a utility increment of 0.013 was assumed to apply for patients receiving ravulizumab based on a Discrete Choice Experiment (DCE) conducted by the company in the UK [66].This increment was applied as an increase in the HRQoL score of the CKD stage related health states of patients receiving ravulizumab i.e. pre-discontinuation patients and patients resuming after relapse. A summary of the utility values used in the company's `worst-case scenario' analysis is shown in Table 16.

Table 16: Summary of utility values used in the company's `worst case scenario' analysis

State	Adults – utility value	Children – utility value	Justification
CKD 0–2	0.895	0.904	EQ-5D values derived from a relevant patient population and model specific health states – adjusted for general population utilities
CKD 3a–3b	0.844	0.852	
CKD 4	0.742	0.750	
CKD 5/ESRD	0.685	0.692	
Transplant	0.685	0.692	
Transplant success	0.827	0.835	
Reduced burden of treatment (ravulizumab increment versus eculizumab)	0.013	0.013	To account for the differences in administration frequencies
Relapse	-0.1	-0.1	Decrement assumed for patients whose treatment progresses
Key: CKD, chronic kidney disease; EQ-5D, EuroQol-5 Dimension, ESRD, end-stage renal disease.			

Adapted from Table 43 of the CS (Appendix N of Document B; page 117)

Points for critique

The ERG considers that informing the HRQoL based on the pooled EQ-5D-3L data from the ravulizumab and eculizumab studies (aHUS-311, C08-002 adults, C08-003 adults -not included in the ITC-, and C10-004) is appropriate and meets the NICE reference case [59]. The ERG had some concerns regarding the company's approach to missing data. In response to ERG points for clarification, question B4, the company clarified that of the 1,575 utility records, 125 (8%) were removed from the mixed effects models that used data on CKD stage due to an unknown or missing CKD stage at the date of utility record. Of these 125 records, 25 pertained to a single patient whilst 49, 21, and 3 patients had 1, 2, and 3 records missing, respectively. The company also highlighted that there were not any substantial differences between patients who had and did not have any utility records removed due to missing data (see Table 7 of the company's response to ERG points for clarification; page 30). Therefore, given the low level of missing data (125/1575 utility records) and the similarity between patients with and without missing data, the company did not attempt to impute missing data and instead based the utility model only on complete records. To demonstrate the robustness of their estimates, the company conducted a scenario analysis employing a Last Observation Carried Forward (LOCF) approach which resulted in very similar estimates with their preferred approach (see Table 8 of company's response to PfC; page 32). The ERG does not expect the missing data to have a material impact on cost-effectiveness results.

The company applied a HRQoL increment on the CKD stage health states of patients receiving ravulizumab. This QALY increment was added to reflect the utility gain attributed to the reduced frequency of regular infusions with ravulizumab compared with eculizumab and amounted to 0.013 (95% CI: 0.007–0.020) based on the company's DCE [66]. The ERG notes that EQ-5D is NICE's preferred instrument for measuring HRQoL, and any potential utility gains under ravulizumab may

have already been reflected in the EQ-5D data collected in the ravulizumab trials. The company's mixed effects model that considered a treatment covariate did not find a statistically significant effect for treatment (see Table 37 of the CS Appendix M to Document B; page 103). Therefore, it is unclear whether it is appropriate to incorporate a QALY increment for ravulizumab treatment in the company's 'worst-case' scenario analysis.

item 9. The company's use of a QALY increment in patients receiving ravulizumab based on a DCE may not be appropriate.

4.2.10 Resource use and costs

In addition to health state-specific costs, the company's model includes costs relating to drug acquisition, drug administration, protective meningococcal vaccination, treatment monitoring, discontinuation, and relapse. The company conducted a systematic search to identify published cost and healthcare resource evidence (see CS Appendix I of Document B). The identified studies reported only US costs and therefore could not be used to inform the company's model.

To calculate the drug acquisition costs per cycle, the model considers both the drugs' dosing schedules and the patient weight distribution. To account for the increasing weight of children less than 18 years old, the company applies a constant 3.2 kg per 6-month increase to the children's baseline weight distribution. This estimate is based on fitting a linear model to growth charts data obtained from the Royal College of Paediatrics and Child Health (RCPCH) UK-World Health Organization (WHO). A cap is also imposed on the children's weight distribution to ensure that the children's overall mean weight does not exceed the overall mean weight of adults. Once children reach adulthood, they are assumed to maintain a constant weight.

In calculating administration costs, the model includes a 15-minute preparation time and infusion time, which differs between eculizumab and ravulizumab, and a combination of specialist nurse and pharmacist time. For patients who respond to treatment, the company assumes that further administrations would be carried out at home through Alexion's homecare programme. For eculizumab, patients are assumed to switch to the homecare programme after their fifth dose, whilst for ravulizumab after the initial loading dose and two subsequent maintenance doses. Based on the company's communications with NRCTC, the company assumes that [redacted] of patients would switch to the homecare programme. No administration costs are considered for these patients as these are covered by the company.

For both treatments, the costs of continuous prophylactic antibiotics were included, as well as meningococcal vaccinations with MenACWY and MenB, which would take place once before the start of the treatment and then every five years for patients remaining on treatment. With regards to

treatment monitoring, the model includes monthly blood tests and testing for complement blockade initially every 3 months and annually after the first year.

For patients who discontinue treatment, the company assumes frequent monitoring in line with the SETS protocol (see Table 44 of the CS Document B for a detailed list of costs). Also, the model assumes that in patients whose disease relapses after treatment discontinuation, patients would present with Acute Kidney Injury (AKI) and would therefore be subject to AKI-related inpatient costs. In the model, these patients reinitiate treatment and, therefore, also incur treatment acquisition, administration, vaccination, and prophylactic antibiotics costs. The total re-initiation costs over a patient's lifetime are applied upfront, after discounting, upon entering the re-initiation health state. Finally, CKD Stage, dialysis, and kidney transplantation costs were based on Kent et al [67], which was identified through a literature review. A summary of the costs applied in the company's model is provided in Table 17.

Table 17: Healthcare and resource use costs.

Health state	Cost	Source/justification
Drug acquisition[a]	First year: Ravulizumab: [redacted] (adults), [redacted] (children) Eculizumab: £352,800 (adults), £168,407 (children)	MIMS [68] Costs are based on patient weight distribution dosing frequency as per their SmPC [35, 36]
Administration costs[b]	Ravulizumab: Average £208 per dose Eculizumab: £195	PSSRU (2019 [69]) Combination of associated nurse specialist (£113) and pharma specialist (£57). Infusion times as per SmPC with additional 1-hour nurse observation time [35, 36]
Meningococcal vaccine	£290	Hampstead Health Pharmacy [70] Combination of MenACWY (£60) and MenB vaccine (£115) (see Table 41 of the CS -Document B; page 137- for further details)
Treatment monitoring	£69.70 (first year per 2-week cycle) £69.57 (after first year per 2-week cycle)	NRCTC [71] NHS ref 18/1[72] NHS 2015. [73]
Discontinuation cost	£98.87 (per 2-week cycle)	SETS protocol [2] NHS ref 18/1 [72] NHS 2015 [73]
Relapse cost	£1,272.84 (per 2-week cycle)	Silver 2017 [74], cost of diagnosis of acute kidney injury, inflation adjusted
Health state costs (per 2-week cycle)		
CKD 0–2	£17.35	Costs are calculated based on annual hospital care costs in the absence of diabetes and cardiovascular complications (Kent et al. [2015]) [67]
CKD 3a–3b	£17.35	
CKD 4	£16.92	
CKD 5/ESRD	£22.61	
Transplant	£1,059.38	
Transplant success	£49.43	
Key: CKD, chronic kidney disease; ESRD, end-stage renal disease; MIMS, Monthly Index of Medical Specialities; NRCTC, National Renal Complement Therapeutics Centre; PSSRU, Personal Social Services Resource Unit; SmPC, summary of product characteristics. **Note:** [a] Drug costs shown exclude VAT, are based on PAS price for ravulizumab and list price for eculizumab (no PAS applies) and assume no discontinuation. [b] Administration costs are only applied to patients who do not receive homecare – [redacted] of patients (funded by Alexion).		

Table adapted from CS, Document B, Table 36.

Points for critique

The ERG believes that all relevant sources of resource use and costs have been considered and the methods used to estimate the cost of treatment with ravulizumab and eculizumab are broadly appropriate. Figure 8 compares the discounted cumulative drug acquisition and total costs for adults receiving ravulizumab over the model's time horizon. It can easily be observed that compared to the drug acquisition costs, all other cost parameters are negligible; therefore, the only cost parameter that is likely to materially impact cost-effectiveness is the treatment price.

Figure 8: Total and treatment acquisition costs for ravulizumab over the model time horizon.

The ERG notes that in HST1, the committee concluded that *"it had not been presented with sufficient justification for the high cost per patient of eculizumab in light of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition."* and that "*the overall cost of eculizumab was materially higher than the overall cost of other highly specialised technologies.*". In response to ERG points for clarification, question B5, the company highlighted that under the company's PAS (% simple discount), ravulizumab is less expensive than eculizumab and could save the NHS a total of £ over a patient's lifetime, or as much as £ across all aHUS patients over the first five years.

The ERG acknowledges that ravulizumab's cost is lower than eculizumab, however it is still a considerably expensive treatment in absolute terms, costing on average around £ per patient in the first year. Also, ravulizumab is currently being considered by NICE for PNH [ID 1457] and therefore research, development, and manufacturing costs of ravulizumab would not need to be recovered solely by aHUS patients.

The high estimates of incremental costs and potential cost-savings for ravulizumab compared with eculizumab depend critically on the company's model structure and, in particular, on the assumptions associated with treatment discontinuation, relapse and re-initiation of treatment. Specifically, the company's model assumes that a high proportion of patients who discontinue treatment would relapse (42.3% for adults and 50% for children), and that all these patients would receive complement-inhibitor treatment for the remainder of their lifetime. The ERG notes that if a lower proportion of

patients relapse, as suggested by Wijnsma et al (2019) [6], or treatment is provided `on-demand' instead of over a lifetime following relapse, the incremental costs and cost-savings of ravulizumab compared with eculizumab would considerably decrease and other model parameters beyond the drug acquisition costs could start having a larger impact on cost-effectiveness.

4.2.11 Summary

Overall, a summary of the key assumptions of this model is provided in Table 45 of the CS (Document B; page 144) and a comparison of the main features of this economic analysis against HST1 in Table 26 of CS (Document B; page 105).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost-effectiveness results of the company's base-case are shown in Table 18. The company conducted a cost-minimisation analysis for their base-case, where ravulizumab was found to be cost-saving compared to eculizumab with incremental costs [redacted] (deterministic) and [redacted] (probabilistic). In response to ERG points for clarification, question B10, the company reviewed and updated the confidence intervals used for some model parameters for the probabilistic sensitivity analysis (See Table 12 of the Company's response to PfC). Although the company did not report the average incremental costs of the updated PSA, the ERG does not expect these changes to have a material impact on cost-effectiveness.

Table 18: Company's base-case deterministic and probabilistic results.

Technologies	Total costs	Incremental costs
Base-case results (Deterministic)		
Eculizumab	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]
Base-case results (Probabilistic)		
Eculizumab	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]

The company also evaluated a scenario where differential efficacy for CKD stage was assumed for ravulizumab and eculizumab. This scenario used the estimated effects from the ITC analysis and resulted in an ICER of £[redacted] per QALY (South-West quadrant of the cost-effectiveness plane with negative incremental costs and QALYs for ravulizumab compared with eculizumab) as shown in Table 19.

Table 19: Cost-effectiveness results of the company's ITC analysis scenario.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; iNMB, incremental net monetary benefit; WTP, willingness to pay.
Notes: Adults represent [redacted] of the combined adult and children population.

Table adapted from CS Document B, Table 51.

5.2 Company's sensitivity analyses

The company conducted several sensitivity analyses to their cost-minimisation base-case (see Table 52 of the CS Document B; page 153 and response to Tables 6 and 10 of the response to ERG points for clarification). Only sensitivity analyses exploring alternative discount rates for costs and model time horizons had a material impact on incremental costs. ravulizumab was found to yield cost savings compared to eculizumab under all analyses. A tornado diagram of the most influential parameters is shown in Figure 23 of the CS. The diagram indicates that the relapse rates for adults and children, the length of the aHUS diagnosis period, and the proportion of patients who discontinue treatment due to misdiagnosis are the most influential parameters.

5.3 Model validation and face validity check

The company describes the model validation process in Section B 3.10 of the CS. The ERG undertook further validation checks and identified some inconsistencies between the results of the ERG's analyses and the company's reported results. In response to ERG points for clarification, question B11, the company corrected a minor technical error in the economic model. No face validity issues were identified with the model.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

A summary of the main issues identified and critiqued in Section 4 along with the Section where the ERG addresses each issue in its additional analyses is shown in Table 20.

Table 20: Summary of the main issues identified by the ERG

	Dealt with in the		

Critique item and description The ERG considers that:		ERGs base case	ERG's Scenario analyses	Area of remaining uncertainty	Significant impact on ICER
item 1	***Discontinuation due to adequate renal response is not included in the company's base-case analysis***	An.1	Sc.3		
item 2	***The rate of relapse following treatment discontinuation may be overestimated in the company's base-case analysis***		Sc.2		x
item 3	***A constant relapse rate may overestimate the proportion of patients who relapse in the long-term***	An.2			x
item 4	***The company's approach to treatment discontinuation may overestimate incremental costs if more than one discontinuation is permitted in clinical practice.***	An.3			x
item 5	***The optimal treatment strategy for complement-inhibitor treatments is uncertain.***			x	Uncertain
item 6	***The generalisability of the populations included in the ravulizumab trials to UK clinical practice is uncertain.***			x	
item 7	***Eculizumab biosimilar treatment are likely to become available within the next five years.***			x	x
item 8	***It is uncertain whether ravulizumab and eculizumab can be considered equally efficacious.***		Sc.1	x	
item 9	***The company's use of a QALY increment in patients receiving ravulizumab based on a DCE may not be appropriate.***		Sc.1b		

6.1 Exploratory and sensitivity analyses undertaken by the ERG

As shown in Table 20, the ERG identified a number of limitations and areas of uncertainty in the company's cost-minimisation and cost-effectiveness analysis. Where the ERG considered that there was a more appropriate alternative approach, modifications were implemented in a cumulative manner and formed part of the ERG's preferred base case (analyses 1 - 3). Areas of remaining uncertainty were explored as sensitivity analyses to the ERG's base case (scenarios 1 - 4). Thorough descriptions of the analyses that form part of the ERG's base case and sensitivity analyses are presented in Section 6.1.1. and Section 6.1.2. respectively, and the impact on the ICER is detailed in Section 6.3.

6.1.1 Building the ERG base case

6.1.1.1 Analysis 1: Inclusion of discontinuation due to renal response in the base-case

As discussed in relation to item 1, the company acknowledged in the CS that current practice is changing, and lifelong treatment is unlikely to be considered standard. However, discontinuation due to adequate renal response does not form part of the company's base case analysis. As a result, the company's base case assumes that patients discontinue treatment only for reasons related to negative

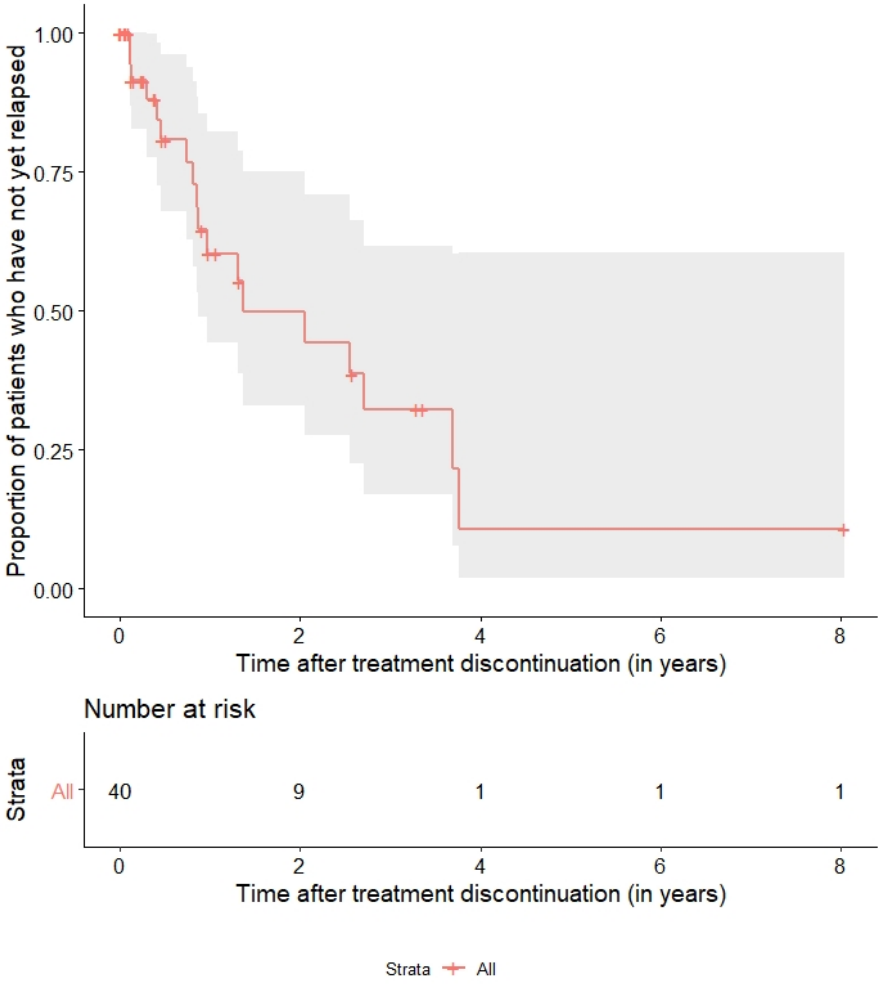
aspects of the treatment i.e. no renal response, AEs, or patient preferences, while potential positive aspects of treatment such as its ability to induce renal response and adequately control the disease are not reflected. The ERG considers it counter-intuitive to consider treatment re-initiation following disease relapse unless renal response is also considered as a viable reason for discontinuation. Furthermore, the evidence supporting lifelong treatment in patients who show renal response is limited, and several case-series studies have demonstrated that treatment can be discontinued after renal response in a large proportion of patients [6]. The evolving literature on this topic has stimulated the design and conduct of an observational study, which is currently ongoing, and aims to demonstrate that patients with adequate renal response can be safely withdrawn from eculizumab treatment and re-introduced only after relapse [45]. Preliminary assessments of the SETS study estimated that around 60-70% of patients would be able to participate in the study after receiving treatment for a minimum of 6 months [2]. Therefore, the ERG incorporates discontinuation due to renal response in the ERG's base-case, assuming that 65% of patients would be eligible for treatment discontinuation due to adequate renal response. The uncertainty around the proportion of patients who would discontinue due to renal response is further explored in scenario 3.

6.1.1.2 Analysis 2: Implementing time-dependent relapse rates after treatment discontinuation

As discussed in relation to item 3, patients who discontinue treatment are subject to disease relapse and treatment re-initiation. To calculate the relapse rates, the company used evidence from the global aHUS registry pertaining to 40 UK patients with a mean follow up of around 3.5 – 4 years. Based on the proportion of patients who relapsed within the follow-up period, the company derived the two-week relapse rate and applied it as a constant rate in all model cycles for the duration of the model's time-horizon. The ERG highlights that this approach does not appropriately deal with censoring, and also assumes that relapse rates are constant through time. The latter is in contradiction to existing evidence suggesting that relapse rates are high shortly after treatment discontinuation and considerably reduced after one year, conditional on sustained remission [6, 20].

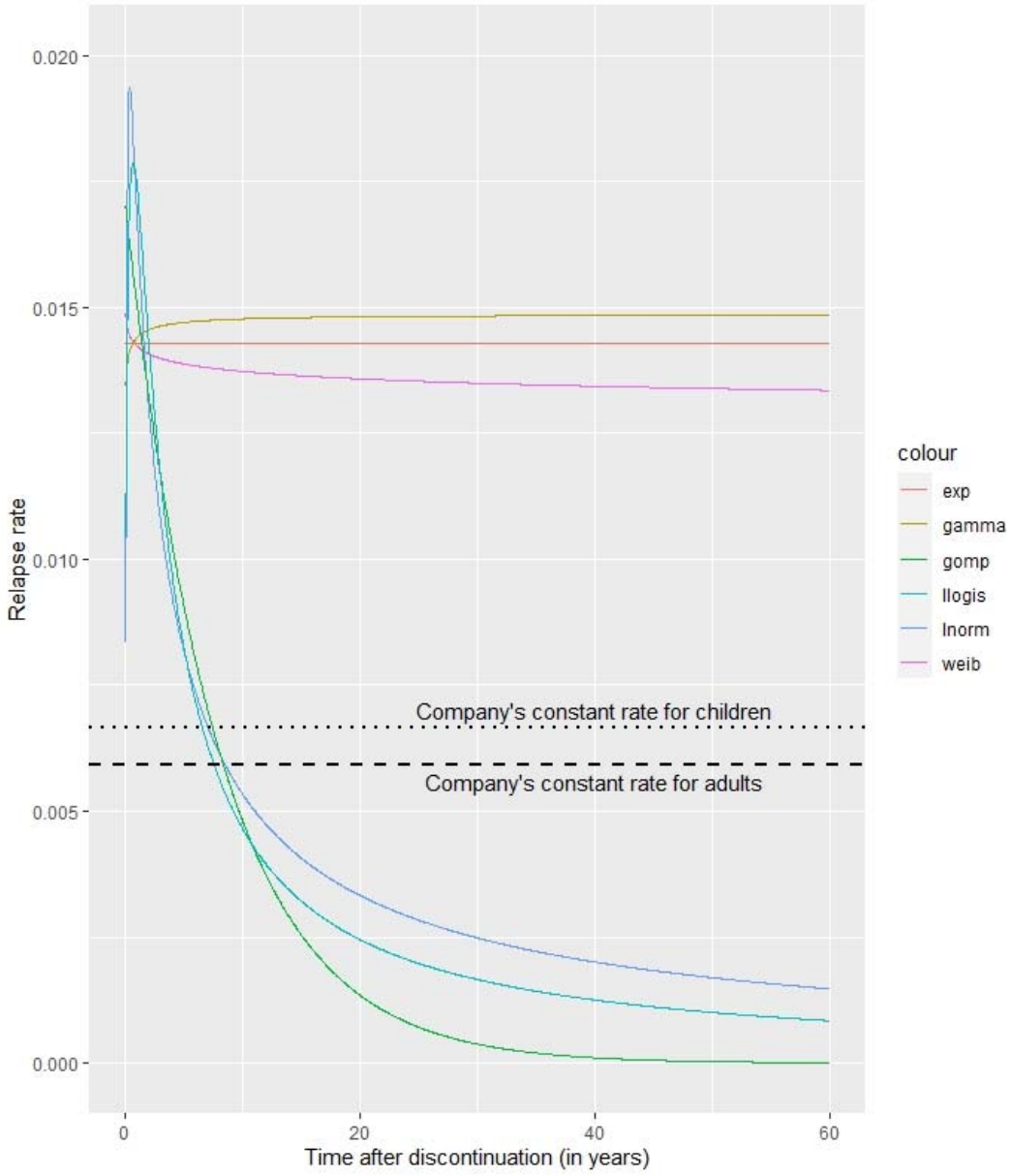
To appropriately account for censoring and to reflect the time-dependent nature of relapse rates, the ERG digitised the evidence provided by the company on the 40 UK patients from the global aHUS registry who discontinued eculizumab treatment and re-initiated following relapse up to April 2020 [37]. Given the low sample size and the fact that the log-rank test did not show a statistically significant difference between adults and children in terms of the probability of relapse (*P-value* = 0.57 – see Appendix B; Figure 11), the ERG pooled the evidence on the two groups and conducted time-to-event analysis in the overall population. Figure 9 shows the Kaplan-Maier data for the combined populations.

Figure 9: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart –All UK discontinued patients in global aHUS registry.



Standard parametric survival models (exponential, weibull, gamma, gompertz, log-normal, log-logistic) were fitted to the data. The models fitted very similarly (see Appendix; Figure 12) with AIC values ranging between 73.3 and 75.3. The extrapolated hazards across the fitted models are shown in Figure 10. The only models that reflected the 'a priori' expectation of decreasing hazard rates through time were the gompertz, the log-normal, and the log-logistic. These models fitted similarly and suggested similar relapse rates over time. As a result, for its base case, the ERG chose the log-logistic model, which sits between the gompertz and the log-normal curves; sensitivity analyses were conducted using the two remaining parametric models.

Figure 10: Predicted relapse rates, per two-week model cycle, over time for different parametric models



6.1.1.3 Analysis 3: Accounting for the potential of multiple treatment discontinuations over the model time horizon

As discussed in item 4, the company's model assumes that patients who discontinue treatment and subsequently experience a relapse will re-initiate lifelong treatment and are not permitted to discontinue treatment again. Although this is in line with current treatment guidelines, some studies have suggested that these patients may be able to discontinue treatment for a second time [6, 39]. The ERG acknowledges that there is a paucity of evidence surrounding second and subsequent treatment discontinuations and highlights that this as an area of considerable uncertainty with high potential impact on incremental costs and cost-effectiveness. To reflect the plausibility of providing treatment `on-demand', the ERG assumed that patients who relapse and re-initiate treatment would receive treatment only for a proportion of their remaining lifetime. This assumption was implemented

homogenously across the model time-horizon by applying a percentage reduction to the treatment acquisition costs incurred at each model cycle following treatment re-initiation. Since it was not possible to know whether and when patients would discontinue for a second time and re-initiate treatment during the course of their lifetime, a constant percentage reduction was applied to drug acquisition costs. Given the uncertainty in the appropriate proportion of patients' lifetime during which patients who relapse will receive treatment, the ERG considered a wide range of possible values from 50% to 100% and presents incremental costs and ICERs resulting from this range. The analysis that is using the 100% value effectively adopts the company's preferred assumption of lifetime treatment, whilst the analysis that is using the 50% value implies that patients who re-initiate treatment would only actually receive treatment for half of their remaining lifetime following a subsequent discontinuation that may or may not, be followed by a second period of treatment re-initiation. Despite the uncertainty in the appropriate value, the ERG considers this a useful approach to provide an indication of the potential impact on lifetime costs from restricting the model structure to permit treatment discontinuation only once.

6.1.2 Scenario analyses to the ERG's base-case

6.1.2.1 Scenario 1: Assuming differential efficacy between ravulizumab and eculizumab

As discussed in relation to item 8, the company assumes in their base case that ravulizumab and eculizumab are equally efficacious. However, due to the lack of randomised evidence comparing ravulizumab and eculizumab directly or with a common comparator, the relative efficacy of ravulizumab compared with eculizumab remains uncertain. Therefore, the ERG conducted sensitivity analysis on the ERG's base case using differential efficacy for CKD stage. This scenario was based on the company's ITC analysis that excluded the four deaths in the ravulizumab group and used propensity score matching methods to balance the treatment groups.

The ERG notes that the company's model also applied an additional utility increment based on a DCE, for ravulizumab to reflect the quality of life gain due to the reduced frequency of infusions. As detailed in item 9, the ERG has some concern regarding the appropriateness of this approach because EQ-5D is the preferred instrument based on the NICE methods guide[59], and the utility gains may already be reflected in the EQ-5D data collected in the ravulizumab and eculizumab studies; although it should be noted that no statistically significant difference in EQ-5D score was found between treatments. Therefore, the ERG conducted the scenario of differential efficacy with and without the utility increment.

6.1.2.2 Scenario 2: Deriving the relapse rate based on all patients included in the aHUS registry

As detailed in relation to item 2, the company's estimate of relapse rate was based on 40 UK patients (26 adults and 14 children) enrolled in the aHUS registry from 2012 onwards who had discontinued

treatment with eculizumab at different time points after treatment initiation. Since 11/26 (42.3%) adults and 7/14 (50.0%) children relapsed over a mean follow up of 3.5 - 4 years, the company assumed that these rates also applied to their base-case. The ERG highlights that these rates are considerably higher than the estimates provided in the literature [6]. The ERG considers a scenario where the evidence on all UK and non-UK patients enrolled in the aHUS registry were considered. This analysis was based on 151 patients who discontinued eculizumab treatment, 30 of whom (i.e. 19.9%) re-initiated treatment over a median follow-up of 2.3 years [55]. Importantly, patients who had an alternative diagnosis (i.e. non-aHUS) as a reason for eculizumab or registry discontinuation were not included, and therefore between-countries variation in the proportion of patients who are initially treated and discontinue due to alternative diagnosis would not affect the estimates. Time-to-event data for the cohort of the 151 patients were not available, therefore, the ERG could not conduct survival analysis to obtain time-dependent relapse rates. As a result, a constant relapse rate was assumed, in line with the assumption of constant rates used in the company's base-case, to enable us to explore the impact of using an estimate of relapse based on data on all patients from the global aHUS registry.

6.1.2.3 Scenario 3: Assuming alternative values for the probability of discontinuing treatment due to renal response

In the CS, the company conducted scenario analyses assuming that 65% and 25% of patients who are still on treatment at 6 months discontinue due to adequate renal response (see Table 52 of the CS Document B; page 153). The impact of this parameter on incremental costs was minimal. This was due to the assumption of a constant relapse rate which implied that, regardless of the proportion of patients who discontinue at 6 months (about 25% under the company's base case and 75% when including renal recovery as a source of discontinuation), most patients are back on treatment - for their remaining lifetime - within 8-10 years (see Section 4.2.3.2 for more details). However, under the ERG's base case relapse rates are time-dependent; therefore, the ERG conducted scenarios to explore whether the impact of the proportion of patients discontinuing due to renal response would be different under time-dependent relapse rates.

6.1.2.4 Scenario 4: Using alternative parametric models to reflect the time-dependent relapse rates

As discussed in Section 6.1.1.2., the ERG's base case implemented time-dependent relapse rates based on a time-to-event analysis that considered the 40 UK patients in the global aHUS registry (as explained in section 6.1.2.2. time-to-event was not available for the non-UK patients in the registry). Three parametric models (log-normal, log-logistic, gompertz) predicted relapse rates for the long-term that broadly aligned with the ERG's and clinical advisor's expectations based on the existing literature. In the absence of adequate evidence to evaluate the plausibility of the three models, the ERG chose the log-logistic model for its base-case and conducted additional scenario analyses using the log-normal and the gompertz models.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

All results for the ERG scenarios are based on deterministic analyses because of the substantial amount of time required to run the model probabilistically. However, the company's deterministic and probabilistic analyses yielded very similar results, suggesting reasonable linearity within the model. The ERG did compare the results of probabilistic and deterministic analyses across a number of scenarios and confirmed that the results were similar.

This section presents the results of the ERG's analyses that formed the ERG's base case in Section 6.2.1. and the results of the ERG's sensitivity analyses, applied to the ERG's base case, in Section 6.2.2. All analyses consider the company's PAS price which offers a [redacted] discount to ravulizumab vials.

6.2.1 Results of analyses building the ERG's base-case

Table 21 illustrates the results of the analyses that the ERG undertook as separate steps to form the ERG's base case. Across all analyses incremental costs remained very high, suggesting that ravulizumab has the potential to result in considerable cost-savings compared to eculizumab. Interestingly, assuming that relapse rates are time-dependent (analysis 2) increased the incremental costs of ravulizumab compared to eculizumab. This was because the estimated relapse rates were higher than the company's constant relapse rates for the first 7.6 years in adults and 6.6 years in children, and lower only thereafter. As a result, in the ERG's base case, 72.6% of adults and 71.3% of children who discontinued treatment were estimated to relapse and re-initiate lifelong treatment within 8 years compared to analysis 1, where 56.8% of adults and 59.8% of children had relapsed and reinitiated lifelong treatment within the same period.

Table 21: ERG's preferred assumptions (ERG base-case)

	Discounted costs (£)		Incremental costs (£)	ICER for RAV vs ECU
	RAV	ECU		
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]
1. Include renal response as a reason for treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Assume time-dependent relapse rates following treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
3. Analysis 2 + Account for the potential of multiple treatment discontinuations (The presented ranges correspond to the cases of receiving treatment after relapse and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime.) **ERG's PREFERRED BASE-CASE**	[redacted]	[redacted]	[redacted]	[redacted]

All analyses were run deterministically. Key. RAV: Ravulizumab, ECU: Eculizumab

The ERG's analysis 3 demonstrates that a second and subsequent treatment discontinuation has the potential to significantly affect the incremental costs of ravulizumab compared with eculizumab. Specifically, if we assume that patients who relapse would not receive lifelong treatment but instead would only receive treatment for 50% of their remaining lifetime, the incremental costs fall to [redacted]. However, despite the considerable reduction in incremental costs, ravulizumab remains cost-saving compared to eculizumab. The ERG highlights that given the assumption of equal efficacy and that ravulizumab is overall less expensive than eculizumab, ravulizumab would most likely remain cost saving under any scenario and the only factor that would affect incremental costs is the actual amount of treatment required throughout a patient's lifetime.

6.2.2 Results of the scenario analyses to the ERG's base-case

The results of the sensitivity analyses that were conducted on the ERG's base case are shown in Table 22. Among the scenarios that considered equal efficacy for ravulizumab and eculizumab (scenarios 2, 3 and 4), only scenario 2 that used a constant relapse rate based on all patients in the global aHUS registry (i.e. including non-UK patients) resulted in a substantial reduction in incremental costs (between [redacted] and [redacted]). [redacted] The only scenario where ravulizumab was not dominant was when differential efficacy was assumed (scenario 1 [redacted] This analysis was based on the company's ITC analysis which used single-arm eculizumab and ravulizumab studies and compared their absolute effects based on propensity score weighting methods. The ERG highlights that the relative efficacy between ravulizumab and eculizumab is highly uncertain and appropriate evaluation of the relative effectiveness would require randomised evidence. However, the rare nature of aHUS poses significant challenges in the acquisition of such evidence.

Table 22: ERG scenario analyses

Scenario	Discounted costs (£)		Discounted QALYs		ICER for RAV vs ECU (Incremental costs, £)
	RAV	ECU	RAV	ECU	
ERG's preferred base-case (i.e. analysis 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Differential efficacy between RAV and ECU (i.e. ITC)					
a) With HRQoL increment applied in the RAV arm based on DCE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Without HRQoL increment applied in the RAV arm based on DCE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Using all 151 patients who discontinued treatment in the global aHUS registry (both UK and non-UK) to derive a two-week relapse rate of 0.37% that is applied as a constant rate throughout the model time horizon for both adults and children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Assuming that only 25% of patients discontinue treatment due to renal response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Using alternative parametric models to derive the time-dependent relapse rates					
a) Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All analyses were run deterministically. The presented ranges correspond to the cases of receiving treatment after relapse and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime. Key. RAV: Ravulizumab, ECU: Eculizumab, DCE: Discrete Choice Experiment, IC: Incremental Costs

*Cost-minimization analysis where QALYs are assumed equivalent between RAV and ECU.

ǂ ICER in the South-West quadrant of the Incremental cost-effectiveness plane with higher values indicating that RAV is more likely to be cost-effective

6.3 Conclusions of the cost effectiveness section

The company submitted a cohort state-transition model that simulates the long-term outcomes of aHUS patients over their lifetime. The model was based on the economic model submitted in HST1 and included health states around treatment discontinuation and sub-health states reflecting aHUS-associated renal function and transplant. Where the model was adapted to reflect the feedback received by the ERG and the committee in HST1, the company outlines these changes in their submission (see Table 26 in the CS Document B; page 105). The ERG considers that the company's approach is appropriate and accurately reflects the decision problem defined in the final NICE scope.

There are, however, limitations and areas of remaining uncertainty (see Table 20). The main areas of uncertainty are: whether patients who respond to treatment and have their renal function restored can safely discontinue treatment and re-initiate only after disease relapse without a considerable risk to the patients' renal function and overall health (item 1); the proportion of UK patients who would relapse following treatment discontinuation and require treatment re-initiation (item 2); whether relapse rate is constant through time or is higher immediately after discontinuation and then decreases over time (item 3); whether complement-inhibitor treatment should be provided only `on demand' i.e. whether patients whose disease is adequately controlled following a relapse and a second treatment course could safely discontinue treatment again (item 4); whether ravulizumab and eculizumab can be considered equally efficacious in the absence of comparative evidence (item 8); whether the evidence of the ravulizumab trials are generalisable to patients expected to be treated for aHUS in the UK (item 6); and finally, whether eculizumab biosimilar treatments, which are expected to become available in the next 5 years should be considered as alternative treatment options (item 7).

To address these issues, the ERG made a number of changes to the company's base-case (see Section 6.1). First, the ERG included renal response as a reason for treatment discontinuation and used preliminary assessments of the SETS study [2] to inform the proportion of patients who discontinue treatment for this reason. Second, instead of a constant rate of relapse which was assumed in the company's model, the ERG conducted time-to-event analysis to derive time-dependent relapse rates based on UK patients enrolled in the global aHUS registry. Finally, given the uncertainty in the plausibility of providing treatment `on demand', - essentially allowing multiple treatment discontinuations -, the ERG presents a range of plausible estimates of incremental cost based on assumptions about the lowest and highest proportion of patients' lifetime during which they may receive treatment after their first relapse (see Section 6.1.1.3.). The ERG's base case was based on the cost-minimisation analysis (due to limitations in the indirect treatment comparison and limited data to inform the relative effectiveness of ravulizumab and eculizumab) and estimated a range of incremental costs between [redacted] per patient; this implies that ravulizumab could offer considerable cost-savings compared with eculizumab in the NHS. However, it must be noted

that it is highly uncertain whether the clinical effectiveness of ravulizumab and eculizumab are equivalent.

Despite the ERG's attempt to address the key uncertainties, limitations in the evidence base mean that some of the uncertainties remain. First, as discussed in Section 4.2.7., there is no comparative evidence assessing the relative effectiveness of ravulizumab and eculizumab. Hence, the plausibility of the company's assumption of equal efficacy is questionable. In the absence of better evidence, the company assessed a scenario assuming differential efficacy employing an ITC approach that sought to match patients in the single-arm ravulizumab and eculizumab trials using propensity score weighting methods. This approach was also carried forward by the ERG in scenario 1a and 1b. [redacted] Indicatively, under the most extreme conditions of ERG's scenario 1 (i.e. where patients who relapsed after a discontinuation received treatment only for 50% of their remaining lifetime [redacted]. Hence, the ERG concludes that although there is uncertainty relating to the relative effect of ravulizumab and eculizumab, given the company's model structure, the decision to adopt ravulizumab is unlikely to be affected by more or better quality relative effectiveness evidence.

The ERG highlights that in the company's model the cost-effectiveness of ravulizumab is primarily driven by the incremental costs; hence, if the incremental costs were considerably reduced, there could be a significant impact in the cost-effectiveness of ravulizumab. This could happen in two main ways: first, if current practice changed and complement inhibitor treatments were given only 'on demand' such as in 6-month courses following a relapse. In such a scenario, some patients may end up receiving treatment only for a small proportion of their lifetime; therefore, much lower quantities of complement-inhibitor treatments would be needed for these patients over their lifetime and the total incremental costs would substantially reduce because the treatment acquisition cost is the main driver of the incremental costs. Second, if a cheaper alternative complement-inhibitor treatment became available, such as an eculizumab biosimilar (see section 4.2.5.). Although outside of the scope of this appraisal, the ERG notes that eculizumab biosimilar treatments are expected to be available in the next 5 years; therefore, given that the market exclusivity for eculizumab (Soliris) for aHUS is set to expire in November 2023 [1], the latter scenario may soon materialise.

Overall, the ERG's preferred base case suggests that ravulizumab is highly cost-effective and none of the ERG's sensitivity analyses suggested otherwise. These conclusions are contingent on a number of key structural assumptions employed by the company that relate to the relapse rates estimates, the plausibility of providing treatment only 'on demand', and the potential of eculizumab biosimilars,

which could offer a discount compared to eculizumab (Soliris), entering the market. Although the current model structure suggests that more evidence on the relative efficacy of ravulizumab compared with eculizumab would be unlikely to impact cost-effectiveness, the ERG highlights that once key structural uncertainties have been addressed, relative efficacy may have a considerable influence on conclusions.

7 END OF LIFE

End-of-life considerations do not apply to this appraisal.

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9 APPENDICES

9.1 Appendix A

Table 23 ERG appraisal of evidence identification for the clinical effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	PARTLY	- Sources of both published and unpublished studies were included in the search. MISSING: - Reference checking of previous reviews or included studies was not reported as a search method. - Trial registers containing ongoing or completed but unpublished studies (e.g. ClinicalTrials.gov) were not searched. - The HTA database was not searched.
Was the timespan of the searches appropriate?	YES	Database inception to 3rd April 2020.
Were appropriate parts of the PICOS included in the search strategies?	YES	aHUS(P) AND various study designs (S). OR aHUS(p) AND adverse events (O).
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	PARTLY	Database search results were restricted to studies published in English.
Were any search filters used validated and referenced?	UNCLEAR	The source of the search terms used to restrict retrieval by study design (Line 5 – 16, Table 1, Appendix D) or by adverse events (Lines 17 and 18, Table 1, Appendix D) is not reported or referenced. Therefore, it is unclear if validated search filters were used in the search strategies.

9.2 Appendix B

Table 24: ERG appraisal of economic evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	The search strategy was missing for EconLit, however the ERG checked and no studies on aHUS patients would have been found with a search via EconLit.
Were appropriate sources searched?	YES	- MEDLINE, Embase, CENTRAL, CDSR, DARE, EconLit, NHS EED, and HTA database. - Relevant conference abstracts from conferences taking place in the past 2 years were searched.

Was the timespan of the searches appropriate?	YES	The databases were searched on 3rd April 2020 and date limits were not applied.
Were appropriate parts of the PICOS included in the search strategies?	YES	aHUS (P) AND Economic evaluations (S) OR costs (O) OR health-state utility values (O)
Were appropriate search terms used?	YES	However, further terms to capture studies about resource use would have increased comprehensiveness.
Were any search restrictions applied appropriate?	PARTLY	Searches were restricted to those studies published in English.
Were any search filters used validated and referenced?	UNCLEAR	Retrieval was restricted to economic evaluations, cost or health related quality of life studies. No references were provided for any study design search filters, therefore it is unclear if validated search filters were used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Figure 11: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart – adult and children UK discontinued patients in global aHUS registry.

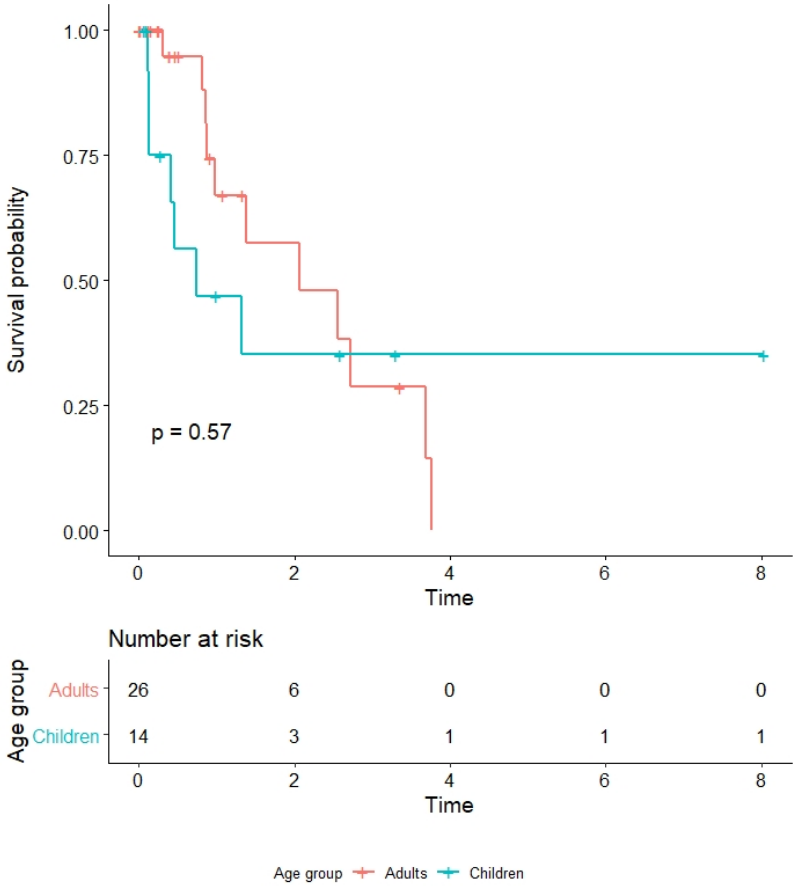
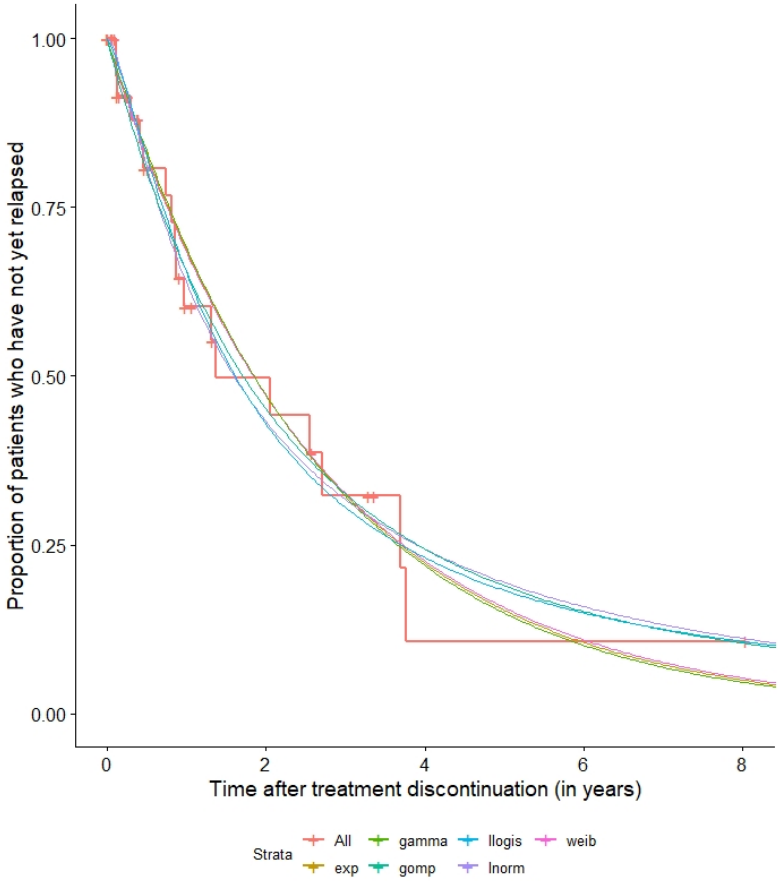


Figure 12: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart – All UK discontinued patients in global aHUS registry. Lines represent the fitted survival models.



National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on insert date** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 Consideration of eculizumab biosimilars

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 12, 13, 15, 20, 23, 24, 90, 102, 111, 112: Consideration of biosimilars which are **not** part of current practice and therefore are not included in the scope of this appraisal is completely inappropriate.	Please delete key issue 7 from Table 1 and Section 1.6 of the report along with all other references to consideration of eculizumab biosimilars.	Not only does any such consideration fall outside of the NICE guide to the methods of technology and the NICE reference case, but we cannot predict the future pathway of care. As noted in the NICE methods guide "The scope provides a framework for the appraisal. It defines the issues of interest (for example, population, comparators, and health outcome measures) and sets the boundaries for the work undertaken by the independent academic groups and the manufacturer(s) or sponsor(s) of the technology who produce reports for the Appraisal Committee." We would request the ERG abides by this framework. We do not dispute that eculizumab biosimilars are in development but there is no guarantee they will enter the UK market and/or on what timeline and/or at what cost. If we were to try and predict the future pathway, several other treatments may also enter the UK market, as acknowledged by the ERG on page 23 but there is no	Not a factual inaccuracy. Despite that, issue 7 of Table 1 has been rephrased to clarify that eculizumab biosimilars are not currently available and are only expected to be available in the near future. Issue 7 in Table 1 now reads: "The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future".

		suggestion that these treatments should also be considered in the submission, which again would be completely inappropriate but would at least reflect a consistent approach to addressing the decision problem by the ERG.	

Issue 2 Treatment discontinuation, relapse and re-initiation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 *"The company's base-case did not consider treatment discontinuation due to adequate renal response."* Page 78: *"However, the company did not include discontinuation due to renal response in their base-case and justified their approach based on the lack of adequate data to inform the proportion of patients who would be eligible for treatment discontinuation due to renal recovery"*	We suggest rewording to *"The company's base-case did not consider treatment discontinuation due to adequate renal response but this was provided in scenario analysis."* *"However, the company did not include discontinuation due to renal response in their base-case and justified their approach based on the lack of adequate data to inform the proportion of patients who would be eligible for treatment discontinuation due to renal recovery and therefore included it in scenario analysis"*	To clarify that Alexion considered renal response within the model and it was provided as a scenario but not considered in the base case.	Not a factual inaccuracy. The ERG report already states that the company considered discontinuation due to adequate renal response only in a scenario analysis. See, for example, page 77 which reads "*Finally, the company did not include discontinuation due to adequate renal recovery in their base-case analysis, but it was included as a scenario analysis."*
Page 76: *"Patients who discontinue due to adequate renal response, do so*	We suggest rewording to *"Patients who discontinue due to adequate renal response, do so only at 6 months after*	Provides clarity on the selection of the 6-month time point	Edited according to company's suggestion.

only at 6 months after treatment initiation, which is the minimum treatment duration for ravulizumab."	*treatment initiation, which is the minimum treatment duration for ravulizumab and in line with the minimum treatment duration within the SETS protocol."*		
Page 77: *"Although the same proportion of patients is assumed to discontinue due to no renal response for both ravulizumab and eculizumab, the time point for discontinuation differs between the two treatments. Specifically, to align with the treatments' corresponding Summary of Product Characteristics, the company assumes that ravulizumab patients without renal response discontinue treatment after 6 months[35], whilst eculizumab patients discontinue after 3.5 months[36]."*	We suggest rewording to *"Although the same proportion of patients is assumed to discontinue due to no renal response for both ravulizumab and eculizumab, the time point for discontinuation differs between the two treatments. Current clinical practice discontinues patients on eculizumab with no renal response after 3–4 months. However, to align with the minimum treatment duration for ravulizumab, outlined in the Summary of Product Characteristics, the company assumes that ravulizumab patients without renal response discontinue treatment after 6 month[35], whilst eculizumab patients discontinue after 3.5 months based on current practice."*	Eculizumab discontinuation time point for patients without renal response was based on clinical opinion and the published reports from the NRCTC, not the Summary of Product Characteristics	Edited according to company's suggestion.
Page 77: *"The company's justification for not including it in the base case is because of the lack of reliable data to inform the proportion of patients who would discontinue after having achieved stabilization, if not normalization, of renal function.*	We suggest rewording to *"The company's justification for not including it in the base case is because of the lack of reliable data to inform the proportion of patients who would discontinue after having achieved stabilization, if not normalization, of renal function. Until the results of the SETS study are produced, clinicians are hesitant to discontinue long-term maintenance therapy in patients with aHUS unless there is a clear*	Provides further clarity on the justification which is not just limited to a lack of data but more importantly the fact that this type of discontinuation is not current practice outside of the SETS study	Not a factual inaccuracy.

	clinical need identified or knowledge of which patients would be suitable for discontinuation"		
Page 78: "*There are several arguments against lifelong treatment. First, there is not adequate evidence to support lifelong treatment in every aHUS patient; instead, there is a growing literature suggesting that aHUS patients who discontinue treatment may not relapse, and that even when they do relapse, treatment is rapidly re-initiated and patients recover their baseline renal function*[39]."	We suggest rewording to "*There are several arguments against lifelong treatment. First, there is not adequate evidence to support lifelong treatment in every aHUS patient; instead, there is a growing literature suggesting that* ***some*** *aHUS patients who discontinue treatment may not relapse, and that even when they do relapse, treatment is rapidly re-initiated and patients recover their baseline renal function*[39]."	To clarify that not all patients discontinue treatment and not all patients who do will avoid relapse	Fakhouri et al., 2017 (1) states that: "*In all patients who experienced a relapse, eculizumab was rapidly resumed, and thrombocytopenia and AKI rapidly resolved. All relapsing patients recovered their baseline renal function without additional CKD or increased proteinuria."* To clarify that this was the case only in Fakhouri et al., 2017 the ERG rephased this passage, so that it now reads: "*There are several arguments against lifelong treatment. First, there is not adequate evidence to support lifelong treatment in every aHUS patient; instead, there is a growing literature suggesting that aHUS patients who discontinue treatment may not relapse, and that even when they do relapse, treatment is rapidly re-initiated and patients could recover their baseline renal function. For instance, in Fakhouri et al., 2017 all relapsing patients reinitiated*

			treatment and recovered their baseline renal function[39].”

Issue 3 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23: *“A further factor impacting the positioning of ravulizumab, not mentioned in the CS, is the likely availability of several biosimilars (oral and subcutaneous treatments)) within the next five years.”*	Removal of the statement per Issue 1 but we would also like to point out that the current wording suggests that oral and subcutaneous biosimilars are likely to be available in the next five years which is incorrect.	Factual inaccuracy.	This statement was confirmed by clinical advisers to the ERG and as such this is not a factual accuracy. As per changes discussed above we have replaced with: *“A further factor impacting the positioning of ravulizumab, not mentioned in the CS, is the likely availability of several intravenous eculizumab biosimilars for aHUS as well as other oral and subcutaneous eculizumab biosimilars which are currently being developed for PNH and may also become available for aHUS patients, potentially within the next five years.”*
`Page 30: *“Results of the quality assessment were only reported for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-*	Please correct to: *“Results of the quality assessment were reported for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 in CS Document B, Appendix D, Section D.3 and for*	Factual inaccuracy. Quality assessment results were also provided for the eculizumab trials used in the ITC as denoted by the NICE submission template.	The sentences were replaced as suggested.

aHUS-312 in CS Document B, Appendix D, Section D.3." *"The CS did not state whether quality assessment was conducted in duplicate and quality assessment results were only reported for the two ravulizumab trials."*	*eculizumab trials used in the ITC in CS Document B, Appendix D, Section D.1.4.8."* *"The CS did not state whether quality assessment was conducted in duplicate."*		
Page 47: *"A median increase of 29 mL/min/1.73 m2 in the estimated glomerular filtration rate (eGFR) from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m2 at the latest cut-off."*	Please correct to: *"A median increase of 29 mL/min/1.73 m2 in the estimated glomerular filtration rate (eGFR) from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m2 at Day 407."*	Factual inaccuracy. eGFR data from the extension period are reported at Day 407.	Edited.
Page 52: *"A median increase of 80 mL/min/1.73 m2 in eGFR from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m2 at the latest cut-off."*	Please correct to: *"A median increase of 80 mL/min/1.73 m2 in eGFR from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m2 at Day 407."*	Factual inaccuracy. eGFR data from the extension period are reported at Day 407.	Edited.
Page 59: Proportion of patients with a mutation and/or auto-antibody identified reported as 70% for aHUS-C10-003	Please correct data to: *11/22 (50%)*	Data transcription error.	Edited.

Page 60: *"The CS does not make clear whether the ITC analyses included data from the primary c-TMA response or the modified c-TMA response outcome in the aHUS-C10-004 trial."*	Please consider rewording or removing this statement.	Factual inaccuracy. As stated in the CS Document B, Section B.2.9.1 "Where there were differences in baseline definitions or outcome definitions, these were standardized prior to analyses. The definitions used in the pivotal ravulizumab trials provided the baseline for standardization" This description of the ITC analyses makes it clear that the c-TMA outcome was aligned to the ravulizumab trial definitions and therefore data from the C10-004 trial would be equivalent to the modified c-TMA response as defined in that trial.	Thanks for clarifying, statement has been removed as suggested.
Table 10, Page 62: Paediatric patients ravulizumab; Age in years: mean SD; Stabilized weights: [redacted]	Please correct to: Paediatric patients ravulizumab; Age in years: mean SD; Stabilized weights: [redacted]	Data transcription error.	Edited.
Page 64: *"…:[redacted]% vs [redacted]%) and systolic blood pressure (after application of stabilized weights…"*	Please correct to: *":[redacted]% vs [redacted]%) and systolic blood pressure (after application of stabilized weights…"*	Data transcription error.	Edited.
Page 92:		Factual inaccuracy.	Edited as suggested by the company.

"Finally, the company's analyses use the evidence reported in ravulizumab and eculizumab studies at 26 weeks and project them through the patients' lifetime. The ERG notes that a period of 26 weeks is adequate to establish that ravulizumab and eculizumab are effective treatments for aHUS…."	*"Finally, the company's analyses use the evidence from the ravulizumab and eculizumab studies at 52 weeks and 5.5 years respectively, and project them through the patients' lifetime…."*	The data used in the model was taken from the ravulizumab and eculizumab studies using the weighted patient level data. The regression analyses used to inform the model transitions were based on the first 52 weeks of data (the prespecified analysis period – maximum follow-up 799 days for 311 and 743 days for 312) for the ravulizumab studies, and 5.5 years for the eculizumab studies (post 5.5 years had very sparse data). There were limited data available after these points in time, leading to the potential for a small number of individuals and data points to disproportionately impact results. (CS Document B Appendix N.1.1, page 107)	

Issue 4 Editorial errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28: *"A **PRIMSA** flow diagram was reported in CS…"*	Please correct to: *"A PRISMA flow diagram was reported in CS…"*	Editorial error.	Edited.
Page 31: *"Diagnosis of aHUS was determined by evidence of TMA (platelet count of < 150,000/µL, LDH ≥ 1.5 × ULN, haemoglobin, ≤ lower limit of normal [LLN], and serum creatinine level ≥ ULN), haemolysis and kidney injury without ADAMTS13 deficiency, Shiga toxin, a positive direct Coombs test or systemic bacterial infection."*	Please correct to: "*Diagnosis of aHUS was determined by evidence of TMA, haemolysis and kidney injury (platelet count of < 150,000/µL, LDH ≥ 1.5 × ULN, haemoglobin, ≤ lower limit of normal [LLN], and serum creatinine level ≥ ULN) without ADAMTS13 deficiency, Shiga toxin, a positive direct Coombs test or systemic bacterial infection."*	Editorial error.	Edited.
Page 31: *"Loading dosages ranged from 2,400mg to 3,000mg and maintenance doses from 3,000mg to 3,600 based on patient body weight, as per the licence indication."*	*Please correct to:* *"Loading dosages ranged from 2,400mg to 3,000mg and maintenance doses from 3,000mg to 3,600mg based on patient body weight, as per the licence indication."*	Editorial error.	Edited.
Page 66: *"Platelet counts were [redacted]% for all transplant and paediatric non-transplant patients."*	Please correct to: *"Platelet count normalisation rates were [redacted]% for all transplant and paediatric non-transplant patients."*	Editorial error.	Edited.

Page 86: *"The population considered by the decision problem is adults and children 10 kg or above with aHUS who are complement-inhibitor treatment-naïve or have received eculizumab for at least 3 months and have shown evidence of response to* ***seculizumab****."*	Please correct to: *"The population considered by the decision problem is adults and children 10 kg or above with aHUS who are complement-inhibitor treatment-naïve or have received eculizumab for at least 3 months and have shown evidence of response to eculizumab."*	Spelling error.	Edited.
Page 97: *"With regards to treatment monitoring, the model includes monthly blood tests and testing for complement* ***blockage*** *initially every 3 months and annually"* after the first year.	Please correct to: *"With regards to treatment monitoring, the model includes monthly blood tests and testing for complement blockade initially every 3 months and annually"*	Spelling error	Edited.
Page 105: *"As discussed in item 4, the company's model assumes that patients who discontinue treatment* ***and*** *and subsequently experience a relapse will re-initiate lifelong treatment and are not permitted to discontinue treatment again."*	Please correct to: *"As discussed in item 4, the company's model assumes that patients who discontinue treatment and subsequently experience a relapse will re-initiate lifelong treatment and are not permitted to discontinue treatment again."*	Word repetition	Edited.

Issue 5 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
ERG Report, Page 31	Patients recruited in the UK not marked as AIC	Patients were recruited across 41 sites in 14 countries ([redacted] patients were recruited in the UK).	Edited.
ERG Report, Page 43	Unpublished trial data not marked as AIC	In Cohort 1, [redacted] patients were screened, enrolled, and treated with ravulizumab (safety set). Of those, three discontinued due to failure to meet eligibility criteria based on laboratory confirmation. The FAS for Cohort 1 included [redacted] patients. [redacted] discontinued treatment due to an AE and the remaining [redacted] completed the Initial Evaluation Period and entered the Extension Period. Of those, one patient discontinued due to physician decision and follow-up of remaining [redacted] was still ongoing as of the latest data cut-off	Edited.
ERG Report, Page 45	Unpublished trial data not marked as AIC	Please mark all data for the extension period in Table 5 as AIC	Edited.
ERG Report, Page 46	Unpublished trial data not marked as AIC	… making a total of [redacted]% (95% CI [redacted]) of patients attaining complete TMA response.	Edited.
ERG Report, Pages 50-51	Unpublished trial data not marked as AIC	Please mark all data for the extension period in Table 6 as AIC	Edited.

ERG Report, Page 51	Unpublished trial data not marked as AIC	…making a total of [redacted]% (95% CI [redacted] complete TMA response rate.	Edited.
ERG Report, Page 52	Unpublished trial data not marked as AIC	A median increase of 80 mL/min/1.73 m2 in eGFR from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m2 at Day 407.	Edited.
ERG Report, Page 52	Unpublished trial data not marked as AIC	In Cohort 1, [redacted]% (of [redacted] patients) reported a ≥3-point improvement in FACIT-Fatigue score	Edited.
ERG Report, Page 58	Unpublished trial data not marked as AIC	[redacted]experienced an AE…	Edited.
ERG Report, Page 63	Published trial data marked as AIC	Therefore, the low mutation rate ([redacted]%) for adult ravulizumab patients…	Edited.
ERG Report, Page 68	Unpublished trial data not marked as AIC	There were a similar proportion of treatment-related adverse events in ravulizumab (ALXN1210-aHUS-311: 20/58 (34.5%), ALXN1210-aHUS-312 (Cohort 1): [redacted] and eculizumab (aHUS-C08-002: 12/17 (71%), aHUS-C10-003: 9/22 (41%), aHUS-C10-004: [redacted] trials. Additionally, there were a similar number of serious adverse events in ravulizumab (ALXN1210-aHUS-311: 33/58 (56.9%), ALXN1210-aHUS-312 (Cohort 1): [redacted] and eculizumab (aHUS-C08-002: [redacted] aHUS-C10-003:	Edited.

		13/22 (59%), aHUS-C10-004: 18/41 (44%)) trials.	
ERG Report, Page 85	Confidential pricing information and results of pharmacoeconomic analyses not marked as CIC	Indicatively, if we were to assume that patients never discontinue treatment, the incremental costs of ravulizumab vs. eculizumab would amount to around [redacted]. In contrast, in the current version of the company's model that allows for only one discontinuation the incremental costs amount to around [redacted].	Edited.
ERG Report, Page 95	DCE data marked as AIC has now been published therefore mark up not necessary	This QALY increment was added to reflect the utility gain attributed to the reduced frequency of regular infusions with ravulizumab compared with eculizumab and amounted to 0.013 (95% CI: 0.007–0.020) based on the company's DCE	Edited.
ERG Report, Page 99	Confidential pricing information and results of pharmacoeconomic analyses not marked as CIC	Please mark Figure 8 as CIC	Edited.

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Technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Thursday 11 February**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Alexion Pharmaceuticals UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Introduction

Alexion would like to thank the Evidence Review Group (ERG) and the NICE technical team for their engagement to date and for further considering our responses to some of the initial concerns highlighted.

Our response comprises five separate parts;

1) Introduction to an increased patient access scheme (PAS) discount

2) Our response to the questions for engagement

3) Additional issues

4) Summary of changes to the cost-effectiveness estimate(s)

5) Appendices

1. Introduction to an increased PAS discount

Alexion is pleased to confirm that an increased PAS discount has been offered to NHS England. A PAS price of £[redacted] per 300 mg ravulizumab (representing a discount of [redacted]% on the list price) has been submitted to reduce the net cost of ravulizumab to £[redacted] and £[redacted], for the 3 mL and 11 mL vials, respectively. [redacted]

The impact of this increased PAS discount on the cost-effectiveness estimates for ravulizumab are fully detailed in Section 4 of this response. With the base-case assumptions from the original submission applied, cost savings are increased by £[redacted], representing absolute per-patient cost savings of £[redacted] to NHS England. Importantly, ravulizumab remains cost saving for all scenarios presented in the original submission and by the ERG, including the ERG's and revised company base-case analyses. Even in the worst-case scenario analysis using differential efficacy for CKD stage alone based on the ITC, ravulizumab remains cost-effective. When applying the revised company base-case assumptions with the output of the ITC applied, ravulizumab reduces costs by [redacted] (a total saving of [redacted]), with a decrease in QALYs of ([redacted]). Therefore, the ICER sits within the South-West quadrant of the cost-effectiveness plane and remains well above the threshold to consider eculizumab more cost-effective than ravulizumab ([redacted]).

It is hoped that this increased discount and additional information provided in response to the ERG issues alleviates any initial uncertainty around the cost-effectiveness of ravulizumab and can enable a positive recommendation at the 13 April 2021 Appraisal Committee Meeting (ACM), enabling rapid patient access to this innovative, cost-saving treatment.

2. Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of the ravulizumab trials to NHS practice	**NO**	Alexion maintains that the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trials are generalisable to NHS practice and reflect both treatment-naïve and eculizumab-responsive aHUS patients; both of whom are eligible for ravulizumab treatment. Although clinical advisors to Alexion and to the ERG expect eculizumab to remain an important first-line treatment for aHUS and ravulizumab to be used in eculizumab-responsive patients in the majority, they do recognise patient groups for whom ravulizumab would be a preferred first-line treatment option. For example, paediatric patients where it is challenging to maintain central lines for a long period of time, patients with a known complement mutation or autoantibodies and patients with a family history of aHUS. Alexion recognises that the number of patients with eculizumab-responsive disease at enrolment is small in the ravulizumab for aHUS clinical trial programme (n=10) and limited to paediatric and adolescent patients (ALXN1210-aHUS-312 trial). However, when considered

		alongside the Extension Phase data from both trials (that reflect an adult and paediatric population with complement inhibitor-responsive disease) and data from the ALXN1210-PNH-302 trial that enrolled eculizumab-stable adult patients with PNH, there is a comprehensive body of evidence supporting the safe and effective 'switching' of patients from eculizumab to ravulizumab. This body of evidence was considered by the European Medicines Agency (EMA) during the regulatory review of ravulizumab and a marketing authorization for the treatment of aHUS, regardless of previous treatment with eculizumab, was considered appropriate.[1] The fact that clinical advisors to Alexion and the ERG expect ravulizumab to be used primarily in eculizumab-responsive patients also suggests they are comfortable applying the ravulizumab trial data to this patient group. Submissions from the British Association for Paediatric Nephrology (BAPN), UK Renal Pharmacy Group and NHS England recognise that ravulizumab would provide an important alternative treatment option for patients with aHUS (without any restriction based on treatment history). While not captured within the top-line summary of the ERG concerns around generalisability, we also want to address comments in the full ERG report that suggest "many" and/or a "significant proportion" of the patients enrolled to the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trials did not have aHUS. These comments appear to be primarily informed by the low prevalence of identified complement mutation or autoantibodies in patients enrolled. As previously detailed, the diagnosis of aHUS is one of exclusion and there is no single test that can confirm a diagnosis of aHUS. Eligibility criteria for enrolment to ALXN1210-aHUS-311 and ALXN1210-aHUS-312 required patients to have evidence of TMA, haemolysis and kidney injury in the absence of factors that confirmed a differential diagnosis or systemic infection that

		could confound an accurate diagnosis of aHUS. This generally aligns with the diagnostic process adopted in the UK. Identification of complement mutation or autoantibodies is not a requirement for diagnosis of aHUS and it is well accepted that some patients diagnosed with aHUS in the UK do not have an identified complement mutation or autoantibody. As previously detailed, published analyses suggest only 45-70% of diagnosed aHUS patients have either a currently identifiable underlying genetic mutation or anticomplement autoantibodies.[2-5] Alexion acknowledges that the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trial populations appear broader than the aHUS population treated with complement inhibitor in the NHS and that there were some patients enrolled who would not be considered eligible for eculizumab in the UK. We have no reason to believe the inclusion of these patients would positively bias the trial outcomes in favour of ravulizumab. If anything, we would expect their inclusion to negatively bias the trial outcomes. For example, clinical advisors to Alexion explained that those patients who died in the ALXN1210-aHUS-311 trial were unlikely to have been considered eligible for eculizumab in the UK given the advanced stage of their disease at presentation.[6] In addition to the low prevalence of identified complement mutation or autoantibodies, the ERG refers to the baseline TMA status of patients in the ALXN1210-aHUS-311 trial as a potential generalisability concern in their report. We would like to reassure the ERG that all patients had evidence of TMA at screening to confirm their eligibility for the trial with respect to a diagnosis of aHUS. However, given the potentially life-threatening nature of TMA, most patients (82.8%) received immediate plasma exchange/plasma infusion treatment before the first dose of study drug which will result in a temporary improvement in platelet and lactate dehydrogenase (LDH)

		levels. Such treatment does not address the underlying pathology of aHUS and the likelihood is that these parameters would revert to initial levels should patients not have gone on to receive complement inhibitor. We do not therefore believe the baseline TMA of patients measured after emergency plasma exchange/plasma infusion treatment reflects a patient group with a more favourable prognosis over the longer-term.
Key issue 2: Relative efficacy of ravulizumab versus eculizumab	**YES**	A randomized controlled trial (RCT) was not considered feasible in the aHUS setting given the rarity and severity of this condition, and in agreement with the EMA, clinical evidence in the PNH setting and pharmacokinetic / pharmacodynamic data in the aHUS and PNH indications are leveraged to support an assumption of equivalence between ravulizumab and eculizumab. Underpinning this clinical evidence and further supporting an assumption of equivalence is the biological heritage of these two complement inhibitor treatments that share 99% homology and the same fundamental mechanism of action. Indeed, the ERG acknowledge that it is clinically plausible that ravulizumab and eculizumab have equivalence efficacy and safety in aHUS patients based on this biological heritage. In the absence of head-to-head data proving equivalence of ravulizumab and eculizumab in the aHUS setting, an indirect treatment comparison (ITC) was conducted, adopting NICE recommended methods to provide as robust an analysis as possible within the evidence base available. Alexion acknowledges there are unavoidable uncertainties around the conclusions of the ITC, but when considered alongside the biological and clinical evidence, we believe an assumption of equivalence is strongly supported. This belief is shared by the clinical community.

		Alexion would however like to take this opportunity to try and alleviate some of the ERG's concerns with respect to the heterogeneity of patients across the ravulizumab and eculizumab trials used to populate the ITC and the ITC outcomes supporting an assumption of equivalence. As confirmed at the technical engagement call, the primary concern in terms of patient heterogeneity is the apparent difference in the prevalence of identified complement mutation or autoantibodies between patients enrolled to the ravulizumab and eculizumab trials as this was a difference not controlled for in the adjusted ITC analyses provided. Although the characteristics considered important for matching in the ITC were selected by expert clinicians and complement mutation or autoantibodies were not raised as an important variable, we acknowledge that clinical advisors to the ERG did highlight this as an important difference. We have therefore further explored the available data relating to the prevalence of complement mutation or autoantibodies, and the potential impact of these factors on clinical outcomes. It is important to acknowledge that genetic testing was not permitted by some ethics committees at some sites and therefore could not be mandated in the study protocols. Genetic testing within trial was thus voluntary and required patient consent so was not "standard protocol". Where genetic testing within trial was conducted, it was in the form of full genome sequencing rather than the standard diagnostic genetic testing; this method cannot pick up some of the more common aHUS-related pathogenic mutations that result from repeat sequences/duplications.

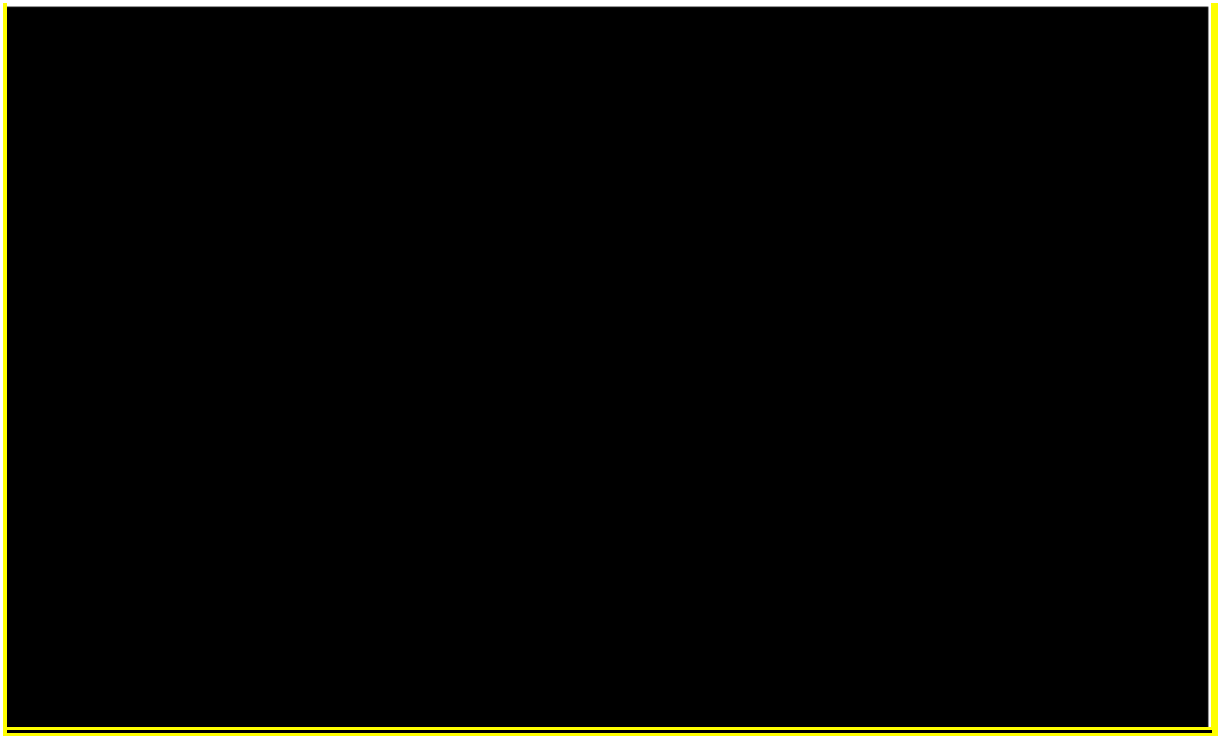
		Given the gaps in these within trial data, study investigators were contacted retrospectively to ask whether diagnostic genetic testing had been conducted in routine clinical practice and whether results of that testing could be shared. Some additional data were made available for the adult population of the ALXN1210-aHUS-311 trial and are provided in the appendices. These data show that [redacted] patients ([redacted]% of the trial population) were not tested for complement mutation or autoantibodies at all; [redacted] of [redacted] patients ([redacted]%) who were tested either in the trial or in clinical practice had an identified complement mutation or autoantibodies. [redacted] of these [redacted] patients ([redacted]%) mounted a complete TMA response in the trial. Of the [redacted] patients who had no identified complement mutation or autoantibodies, [redacted] ([redacted]%) mounted a complete TMA response in the trial. The similar complete TMA response rates across these groups support the generalisability of trial outcomes to the UK population despite a potential difference in the prevalence of identified complement mutation or autoantibodies. With respect to the ITC outcomes more generally, we agree with the ERG that it is difficult to draw conclusions on the significance of any differences observed, but maintain that there are no clear trends favouring one treatment over another. The fact that the 'differential efficacy' scenario uses an outcome that numerically favours eculizumab rather than ravulizumab should be considered a conservative scenario when considering the totality of evidence supporting an assumption of equivalence. Importantly, when CKD stage outcome data from the ITC are used to model a 'differential efficacy' scenario in the economic modelling, ravulizumab remains cost-saving to the NHS. At the technical engagement call, the ERG confirmed this was the case but noted that this scenario analyses assumed a life-long treatment duration. However, Table 22 of the ERG

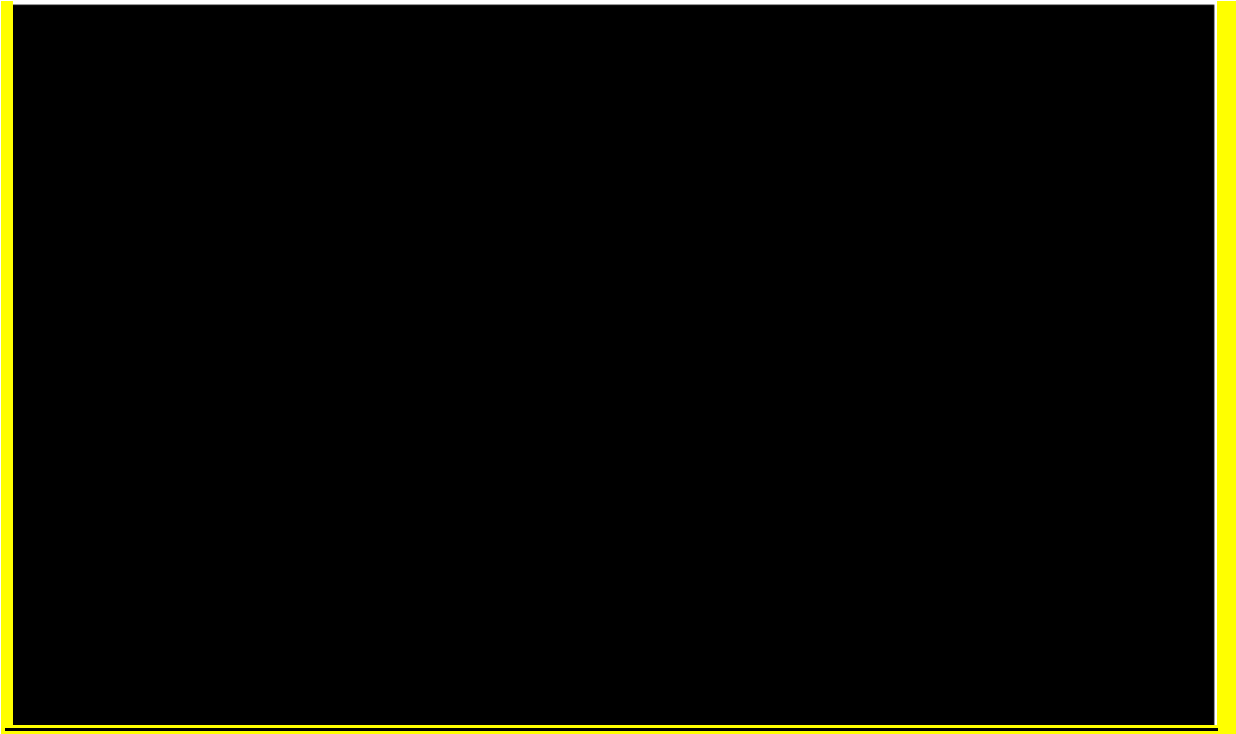
		report presents the results of a scenario which explores the application of a differential treatment effect and a shorter-term treatment duration. In this scenario, CKD stage outcome data from the ITC were applied, and the proportion of time that patients spend on treatment following re-initiation of ravulizumab or eculizumab post-relapse was varied consistent with the ERG's analysis 3 presented in Section 6.1.1.3 of the ERG report. This scenario reported cost savings ranging from £[redacted] to £[redacted] as the proportion of time spent on treatment increases from 50% to 100% respectively. However, these cost savings have now increased further with the introduction of the revised confidential PAS, with cost savings now ranging from £[redacted] to [redacted]. As this scenario estimates a decrease in QALYs of [redacted] or [redacted] (including/excluding the additional utility increment associated with ravulizumab), the ICER sits within the South-West quadrant of the cost-effectiveness plane, with higher ICER values indicating that ravulizumab is more likely to be cost-effective. The ICERs now range from [redacted] to [redacted] with the additional utility increment associated with ravulizumab included and [redacted] to [redacted] when this is excluded, and therefore remain well above the threshold to consider eculizumab more cost-effective than ravulizumab for all scenarios. The ERG noted that under the most extreme conditions of this scenario (i.e. where patients who relapsed after a discontinuation received treatment only for 50% of their remaining lifetime), ravulizumab would have to offer less than 2 QALYs overall (i.e. [redacted] QALYs less than its current estimate of [redacted] QALYs) to yield an ICER around £40,000 per QALY. With the revised PAS applied, ravulizumab would have to offer [redacted] QALYs overall (i.e. [redacted] QALYs less than its current estimate of [redacted] QALYs) to yield an ICER around £40,000 per QALY

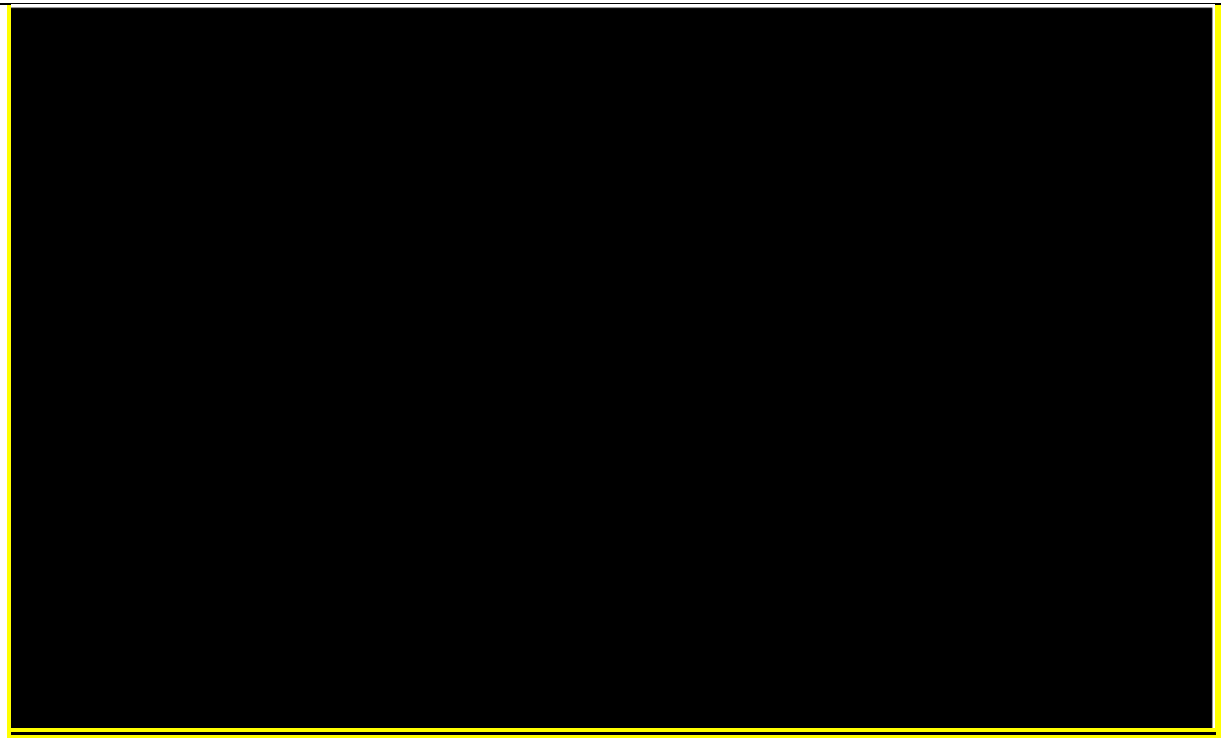
		These scenarios are extremely pessimistic. Firstly, the ERG reduced treatment costs to capture a scenario where patients do not receive life-long treatment, but this is not in line with the treatment approach used in current clinical practice which was modelled in the company's base-case consistent with NICE methods guidance and the reference case. Secondly, this scenario applies differential efficacy but does not account for whether patients are actively receiving treatment in each model cycle. To address this an alternative to the ERGs approach has been explored where QALYs are also adjusted to account for the proportion of time patients spend on treatment following relapse. In this scenario, the total QALYs accrued in the relapsed and on treatment health states were set to be equal between the two arms for the proportion of time that patients were assumed to spend off treatment. This scenario results in a decrease in QALYs of [redacted] or [redacted] (including/excluding the additional utility increment associated with ravulizumab). This improves the cost-effectiveness of ravulizumab as the ICERs, which sit within the South-West quadrant of the cost-effectiveness plane, now range from [redacted] to [redacted] with the additional utility increment associated with ravulizumab included and [redacted] to [redacted] when this is excluded. Therefore, these scenarios provide further reassurance that ravulizumab would remain cost-effective to the NHS even if potential changes to future clinical practice resulted in a reduction in long-term treatment duration. It should also be acknowledged that this differential efficacy scenario utilises an ITC outcome that numerically favoured eculizumab and directly impacts quality-adjusted life year (QALY) estimates, but other outcomes numerically favoured ravulizumab (e.g. eGFR and reduction in LDH from baseline) but do not directly impact QALY estimates.

		Alexion strongly believe the effect of these complement inhibitor treatments would be equivalent in practice when considering the totality of evidence previously described, and that the only real difference for patients treated with ravulizumab rather than eculizumab will be a reduced treatment administration burden that will positively impact their quality of life. We therefore consider this scenario a conservative estimate of the benefit of ravulizumab treatment and its cost-saving potential.
Key issue 3: Long-term efficacy and safety of ravulizumab	**YES**	Data up to 52 weeks are available from the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trials at this time and are provided in the company submission. Extension Periods are ongoing but as per protocol, patients are discontinuing from the study as ravulizumab becomes commercially available. Therefore, while we are expecting final analyses of both trials at 'study end' that will provide additional follow-up, it is difficult to predict when this will happen. It is also unclear what length of follow-up will be available given the permitted variability for individual patients. We have recently shared confidential 104 week data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials with NICE and there are longer-term patient and clinician reports of ravulizumab use in the PNH setting (up to 5 years); these evidence show that ravulizumab is effective with an acceptable safety profile over the longer-term and provides comparable outcomes to those observed in long-term eculizumab data. We do have longer-term safety data from ravulizumab use across various clinical settings available from post-launch Periodic Safety Update Reports (PSURs), the latest of which is provided as a confidential reference alongside this response.[7] The cumulative estimated exposure to ravulizumab since its International Birth Date of 21 December 2018 through 30

		June 2020 is 1529.4 patient-years. No new signals or risks related to the use of ravulizumab have been observed and no actions have been taken for safety reasons further to post-marketing experience with ravulizumab. In the absence of long-term efficacy and safety data for ravulizumab specific to the aHUS setting, eculizumab data are utilised in the economic modelling. These data are considered an appropriate proxy given the biological similarity and assumed equivalence of ravulizumab and eculizumab, as previously discussed.
Key issue 4: Relapse rate following treatment discontinuation	**Yes**	The ERG highlight evidence from the literature which suggests that the risk of relapse is higher shortly after treatment withdrawal and is substantially reduced after around one year of sustained disease control, and therefore conclude that assuming a constant risk of relapse may be inappropriate. Although the approach presented in the original submission was intended to be a simplifying assumption, Alexion agrees that the rate will likely vary to some degree over time in reality and believe that the ERGs preferred approach of applying time-dependent relapse rates is appropriate. Therefore, the ERGs scenario has now been incorporated into the revised company base-case analysis (Section 4). Additionally, the ERG flagged that they did not have access to the full aHUS registry data and were therefore unable to generate time-dependent relapse rates from the population which includes patients both inside and outside of the UK. Although Alexion believe that the UK data is the most appropriate source given it best reflects the decision problem as the data is more likely to be reflective of UK clinical practice, an additional scenario has been provided which uses data from the full population of the global registry, which includes 326 adults and 173 children (Figure 1). Consistent with the ERG's analysis of the UK data, the log-rank test did not

		show a statistically significant difference between adults and children in terms of the probability of relapse (P-value = 0.2). Therefore, extrapolations were generated using data from the pooled population rather than the separate patient groups, consistent with the approach that was adopted by the ERG. **Figure 1. Global aHUS registry Kaplan-Meier data: time from treatment discontinuation to restart (all discontinued patients)** 

		Standard parametric survival models (exponential, Weibull, generalised gamma, Gompertz, log-normal, log-logistic) were fitted to the data (Figure 2). All models, excluding the exponential curve, were consistent with the ERG's stated 'a priori' expectation of decreasing hazard rates through time (Figure 3). **Figure 2. Global aHUS registry extrapolated curves: time from treatment discontinuation to restart (all discontinued patients)**  **Figure 3. Global aHUS registry hazards over time: time from treatment discontinuation to restart (all discontinued patients)**

		 The results from this scenario analysis, which applies curves estimated from the global aHUS registry data rather than from the UK aHUS data (presented in Table 2), demonstrate that ravulizumab consistently remains a cost-saving treatment even with these alternative curves applied. This remains the case even as the generalised gamma and Gompertz curves are applied, which predict a large duration of time until re-initiation of treatment as these curves put a significant amount of weight on latter parts of the Kaplan-Meier data where there are limited numbers at risk. These curves are implausible as they predict that a proportion of patients will

		never relapse and re-initiate treatment during their lifetime which is not consistent with clinical opinion. Following an assessment of the data we believe the Weibull, log-logistic and log-normal curves provide plausible long-term extrapolations. Therefore, we think these curves are worth considering in a scenario analysis, but still believe on balance that the analysis of the UK registry data that the ERG presented is the best option for the base-case analysis given it best reflects the decision problem as the data is more likely to be reflective of UK clinical practice. However, regardless of the approach adopted, the results are broadly consistent and continue to demonstrate that ravulizumab remains a cost-saving treatment option.
Key issue 5: Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations.	**NO**	An 'on demand' treatment approach that allows for multiple treatment discontinuations is not an established treatment approach in current practice and there are no robust data supporting such a treatment approach. Alexion agrees with the ERG that the ongoing Stopping Eculizumab Treatment Safely in aHUS (SETS) study is expected to influence treatment approach in future, and we have always reflected this in our discussion of the pathway of care and in our modelling approach (see response to Key issue 6). However, it is important to acknowledge that the SETS study is not designed to assess multiple treatment discontinuations; rather, it is designed to assess the safety and impact of a single treatment discontinuation and patients who relapse following discontinuation and require re-introduction of eculizumab will remain on treatment for the remaining term of the study.[8]

Key issue 6: Treatment discontinuation due to renal response	**YES**	As acknowledged above, Alexion has always been transparent in our discussion of the pathway of care and that the SETS study is expected to influence a change in future practice such that lifelong treatment will no longer be the standard treatment approach for patients who demonstrate good renal recovery. Our base case modelling approach was to reflect the current treatment approach in line with NICE methods guidance and the reference case; however, this predicted future treatment approach was included in a scenario analysis whereby patients with renal response discontinued treatment but on relapse, reinitiated treatment and remained on treatment indefinitely. The ERG has shared two main concerns with this scenario analyses in their report and on further discussion at the technical engagement call (i) that the number of patients reinitiated on treatment seemed high (50%) if discontinuation due to adequate renal response is excluded and (ii) that the assumption patients would remain on treatment indefinitely following reinitiation was not robust. On the first point, the scenario analysis presented in the company submission that has been adopted in the ERG and revised company base-case analysis which includes discontinuation due to adequate renal response, only results in modest reductions in the cost savings of ravulizumab versus ecuzliumab. This scenario resulted in incremental costs changing from [redacted] to [redacted] with the original PAS discount applied, which becomes a change from [redacted] to [redacted] with the revised PAS discount factored in. On the second point, the ERG have themselves explored a range of scenarios varying the proportion of time that patients spend on treatment following relapse and re-initiation. The results of this analysis demonstrated that ravulizumab remains a cost-saving treatment option,

		even in the ERGs most pessimistic scenario of 50%, with this saving now increasing further as a result of the revised confidential PAS discount. With this new PAS applied, even if the proportion of time patients spend on treatment following relapse is reduced down to [redacted], ravulizumab remains a cost-saving treatment option. These results demonstrate that even if clinical practice was to change in the future and therefore impact the time that patients spend on treatment, ravulizumab remains a cost saving option, given its lower drug acquisition cost due to the availability of the revised confidential PAS and because any changes in future treatment approach would apply equally to both patients receiving ravulizumab or eculizumab. We would also like to take this opportunity to notify NICE and the ERG that the 2019/2020 annual report from the National Renal Complement Therapeutics Centre (NRCTC) is now available.[9] During the reporting period of April 2019 until March 2020, 36 patients were initiated on eculizumab; 8 patients (22%) subsequently discontinued due to differential diagnosis, 13 patients (36%) discontinued treatment due to lack of renal recovery and 15 patients (42%) remain on treatment.
Key issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future	**NO**	Eculizumab biosimilars are not part of the current pathway of care and are not included in the scope of this appraisal that as per the NICE methods guide "sets the boundaries for the work undertaken by the independent academic groups and the manufacturer(s) or sponsor(s) of the technology who produce reports for the Appraisal Committee". Alexion cannot and should not be asked to predict new treatments that may enter the future pathway of care. NICE representatives at the technical engagement call supported this viewpoint and confirmed that NICE will not consider the potential impact of biosimilars at the committee meeting. Alexion therefore assume this issue is resolved and will not be discussed further.

3. Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Ravulizumab vial size	Not applicable	NO	Alexion would like to take this opportunity to update NICE that the ravulizumab 100 mg/mL vial sizes are now approved for use and will be the vial sizes launched in the UK. As noted in our company submission, the increased drug concentration in these 100 mg/mL vials reduces the infusion times for ravulizumab such that they are generally in line with those of eculizumab.[10] Although the ERG highlighted no issues relating to the ravulizumab vial sizes, we wanted to acknowledge a couple of comments in the aHUS Alliance Global Action Experience and Expectations Report provided as part of the technical engagement papers that suggest the infusion time for ravulizumab was longer than for eculizumab. These comments are based on the 10 mg/mL vial size that will not be launched in the UK and therefore are not relevant to ravulizumab infusion times patients will experience in NHS England.

4. Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case Incremental costs
Original company base-case ICER (with revised PAS)			[redacted]
Issue 6	Renal response excluded as a reason for treatment discontinuation	Renal response included as a reason for treatment discontinuation	[redacted]
Issue 4	Constant relapse rate applied following treatment discontinuation	Time-dependent relapse rates applied following treatment discontinuation	[redacted]
Revised company base-case			[redacted]

In addition to the change reported above, we have introduced an increased PAS discount as described in Section 1 to the economic analyses. The impact of this increased PAS discount on the company's preferred cost-effectiveness estimates and the ERG's preferred cost-effectiveness estimates, and key scenarios are detailed in the tables below.

Table 1: Company and ERG's preferred analysis – updated PAS (ERG report, Table 21)

	Orignal PAS discount			Increased PAS discount			
	Discounted costs (£)		Incremental costs (£)	Discounted costs (£)		Incremental costs (£)	Impact
	RAV	ECU		RAV	ECU		
Original company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Cost savings have increased by [redacted]
ERG analysis 1: Include renal response as a reason for treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Cost savings have increased by [redacted]
ERG analysis 2: Analysis 1 + Assume time-dependent relapse rates following treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Cost savings have increased by [redacted]
ERG's PREFERRED BASE-CASE: Analysis 2 + Account for the potential of multiple treatment discontinuations (The presented ranges correspond to the cases of receiving treatment after relapse	[redacted] to [redacted]	[redacted] to [redacted]	[redacted] to [redacted]	[redacted] to [redacted]	[redacted] to [redacted]	[redacted] to [redacted]	Cost savings have increased by [redacted] to [redacted]

and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime.)							
REVISED COMPANY BASE-CASE: Include renal response as a reason for treatment discontinuation Assume time-dependent relapse rates following treatment discontinuation using UK cohort from aHUS registry	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Cost savings have increased by [redacted]

Table 2: Key company scenario analysis

Scenario		Incremental costs (£)	Change from base case incremental cost (£)
REVISED COMPANY BASE-CASE:		[redacted]	
Company scenario: Time-dependent relapse rates following treatment discontinuation using full global cohort from aHUS registry	Log-logistic	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]

Table 3: Key scenario analysis – updated PAS (ERG report, Table 22)

Key scenario analysis (Increased PAS)	Discounted costs (£)		Discounted QALYs		ICER for RAV vs ECU (Incremental costs, £)	iNMB (WTP £30,000)	Impact
	RAV	ECU	RAV	ECU			
ERG's preferred base-case	[redacted] to [redacted]	[redacted] to [redacted]	-*	-*	[redacted] [redacted] to [redacted])		
1. Differential efficacy between RAV and ECU (i.e. ITC) • With HRQoL increment applied in the RAV arm based on DCE	[redacted] to [redacted]	[redacted] to [redacted]	[redacted]	[redacted]	[redacted] to [redacted] #	[redacted] to [redacted]	[redacted] [redacted] [redacted] to [redacted]
• Without HRQoL increment applied in the RAV arm based on DCE	[redacted] to [redacted]	[redacted] to [redacted]	[redacted]	[redacted]	[redacted] to [redacted]	[redacted] to [redacted]	[redacted] [redacted] [redacted] to [redacted]

2. Using all 151 patients who discontinued treatment in the global aHUS registry (both UK and non-UK) to derive a two-week relapse rate of 0.37% that is applied as a constant rate throughout the model time horizon for both adults and children	[redacted] to [redacted]	[redacted] to [redacted]	-*	-*	[redacted] to [redacted]	-*	[redacted] to [redacted]
3. Assuming that only 25% of patients discontinue treatment due to renal response	[redacted] to [redacted]	[redacted] to [redacted]	-*	-*	[redacted] to [redacted]	-*	[redacted] to [redacted]
Using alternative parametric models to derive the time-dependent relapse rates • Log-normal • Gompertz	[redacted] to [redacted]	[redacted] to [redacted]	-*	-*	[redacted] to [redacted]	-*	[redacted] to [redacted]

	[redacted] to [redacted]	[redacted] to [redacted]	-*	-*	[redacted] to [redacted])	-*	[redacted] to [redacted]
Company scenario: Costs and QALYs are adjusted to account for the proportion of time patients spend on treatment following relapse (further details provided in key issue 2 response) (The presented ranges correspond proportion of time patients spend on treatment following relapse: 50% and 100% of a patient's remaining lifetime) • With HRQoL increment applied in the RAV arm based on DCE	[redacted] to [redacted]	[redacted] to [redacted]	[redacted]	[redacted]	[redacted] to [redacted]#	[redacted] to	-
	[redacted] to [redacted]	[redacted] to [redacted]	[redacted]	[redacted]	[redacted] to [redacted]#	[redacted] to [redacted]	-

• Without HRQoL increment applied in the RAV arm based on DCE							

Key: iNMB, incremental net monetary benefit; WTP, willingness to pay; RAV, Ravulizumab; ECU, Eculizumab; DCE, Discrete Choice Experiment; IC, Incremental Costs

Notes: The presented ranges correspond to the cases of receiving treatment after relapse and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime.

*Cost-minimization analysis where QALYs are assumed equivalent between RAV and ECU.

#ICER in the South-West quadrant of the Incremental cost-effectiveness plane with higher values indicating that RAV is more likely to be cost-effective

5. Appendices

Table 4: Patient-level complement mutation or autoantibodies analyses from the ALXN1210-aHUS-311 trial

Patient ID	Trial genetics testing[a]	Clinician genetics testing[b]	Classification[c]	cTMA response
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Trial genetics testing[a]	Clinician genetics testing[b]	Classification[c]	cTMA response
15	[redacted]	[redacted]	[redacted]	[redacted]
16 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
28 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Trial genetics testing[a]	Clinician genetics testing[b]	Classification[c]	cTMA response
31	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
37	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]	[redacted]
40 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
41	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]
45 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Trial genetics testing[a]	Clinician genetics testing[b]	Classification[c]	cTMA response
47	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
49	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]
51 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]
53 (KTx)	[redacted]	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]	[redacted]
55	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]

Key: cTMA, complete thrombotic microangiopathy; EP, cTMA response in the Extension Phase; KTx, kidney transplant patient.
Notes: [a], data collected within the ALXN1210-aHUS-311 trial via full genome sequencing for those patients who consented; [b], data collected retrospectively from study investigators via diagnostic genetic testing conducted in routine clinical practice; [c], classification considers data available from trial genetics testing and clinician genetics testing.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Thursday 11 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with aHUS and current treatment options	
About you	
1.Your name	**Christopher Reardon**
2. Are you (please tick all that apply):	☑ a patient with aHUS? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with aHUS? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	aHUS alliance Global Action
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☑ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☑ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ ✓ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ ✓ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with aHUS? If you are a carer (for someone with aHUS) please share your experience of caring for them.	Between February and May in 2016 I visited my GP on 4 occasions complaining of extremely low energy levels, coughing up large amounts of fluid and the gasping sensation of downing when I was laying on my back. On the 2nd of the visits, they prescribed antibiotics as they thought it was a chest infection. After this didn't clear it up, I returned and demanded they took this more seriously, so they sent me for a chest x-ray. The GP called back and said they couldn't see anything on the x-ray and think its still a chest infection and I should feel better soon. A few days later I woke up and my eyesight had become extremely blurry and by this point I couldn't walk more than a few steps without having to rest. I then sternly called the GP again, demanded he took a closer look at that this wasn't a chest infection. He was shocked by my efforts to walk to his office, then finally took my blood pressure and asked me to do a urine sample. He then informed me I had kidney failure and told me to get the bus to hospital. On arriving at hospital in Kingston Upon Thames on the 2nd of May, i was treated for high blood pressure and admitted to intensive care while the doctors tried to diagnose my situation. While I was there, I suffered a seizure and a few strokes, impacting the control of my muscles on the right side of my face. In the meantime, the doctors had sent some of my bloods to UCLH for review and after spending approx.9 days at Kingston, I was moved across London to UCLH for specialist care. I spent the next 2 weeks having regular plasmapheresis in intensive care and it was during that time, I was given a diagnosis of aHUS.

	By the end of May I was moved onto a ward at UCLH, my eyesight had started to return and I could almost open my right eye again. I had my first does of Eculizumab while on the ward and returned home on the 10th of June. I have been on Eculizumab ever since, returning to UCLH for treatment every 2 weeks. I also take blood pressure medication daily. Over the past 4.5 years it's been a very slow recovery, my EGFR is up from 16 to almost 45. My energy levels have slowly increased, and I've returned to playing golf again without the need for a day off to sleep afterwards. Although my level of fatigue is very unpredictable from one day to the next, so plans are often only "pencilled in". Life decisions have to be made based on the timing & proximity of treatment. This includes my work contracts, my wife's promotions, relocation desires and general family activity plans i.e. weekends away, holidays etc.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for aHUS on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	**7a.** I think the treatment & care at the hospital where I have treatment is fantastic. After almost 5 years of regularly visiting there for treatment, I have found them consistently professional, respectful, and vigilant, but with a real personal touch. They always ask about my wife and son, often by name and whenever I have seemed "not my usual self" or consciously worried about my health, they always get someone to come and check me over and send me off for tests if required. In the past, when other regular patients had unfortunately succumb to their illness, the nurses have recognised that I had made a personal relationship with the patient, informed me of their decline and comforted me on their passing. The "care" from the GP I feel is appalling. They never did (or do) basic observations like blood pressure, which I feel could have raised red flags earlier and prevented the extent of the damage incurred, especially to my kidneys & eyesight. If they listened better to my symptoms, I don't think I'd have been repeatedly told I had a chest infection. And the utter lack of compassion is disgraceful. i.e. when he told me I had kidney failure and had to go to Kingston hospital, I asked if he could help me get there, because I couldn't walk or see. He told me to go across the road and wait for a bus. Also on a later (unrelated to aHUS) visit to the GP after my wife and I had gone through 3 miscarriages, we went for help, and after describing what had happened, his first words were "and . . .what do you want me to do about it".

	7b. I feel incredibly lucky to have been diagnosed in a time when Eculizumab was available on the NHS. When I hear other patients talk about life before Eculizumab, I know the treatment regime would have been frightening, debilitating and with such a low initial kidney function, I fear I would not be alive today. I have also spoken to people on Ravulizumab, and I do have to say, I envy their increased freedom that the added time between treatment offers.
8. If there are disadvantages for patients of **current NHS treatments** for aHUS (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Physically, I do not find the treatment uncomfortable, although I may have got used to it over the past 5 years. I do however feel very washed out / listless for the rest of the day post treatment. It has also become increasingly time consuming and uncomfortable over the past year with Covid, having to make an extra visit to be tested for Covid 2 days before my treatment. Emotionally, the frequent trips to hospital and needle bruises on my arms are a constant reminder of my illness and can often make me feel quite miserable. Economically, I am self-employed, and I spend circa. 20% of my working month unable to work due to treatment and/or covid testing appointments. This drop in availability, coupled with a geographical tie to the treatment location has impacted my ability to earn quite considerably.
Advantages of this treatment	
9a. If there are advantages of ravulizumab over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	While I do not feel in a position to comment on the clinical advantages, the extended time between treatment would mean the following: • Reduced travel costs, I currently spend approx. £140 a month on travel for treatment. This would reduce to an average of £35 a month with ravulizumab. This would equal a saving of £1,260 a year. • I could get more types of work (often jobs require last minute international travel) • My overall availability to work would rise from circa. 80% to almost 97% • My wife could finally accept the promotion at work that requires significant travel.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does ravulizumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	• I also think that having 7 weeks away from a hospital at a time, would have a huge positive impact on my mental wellbeing. • We could start going on holiday for longer than 10 days at a time. The positive impact on my mental wellbeing I feel would be the most important. After almost 5 years of living in a "week on, week off" mentality around treatment, I find it can be mentally quite debilitating. The 7 week break between treatments would provide a very welcome window of not having to be reminded of, or adapt my life around this disease.
Disadvantages of this treatment	
10. If there are disadvantages of ravulizumab over current treatments on the NHS please describe these? For example, are there any risks with ravulizumab? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	I do not see any disadvantages to ravulizumab, my only concern is the lack of evidence for efficacy in patients switching over from eculizumab.
Patient population	
11. Are there any groups of patients who might benefit more from ravulizumab or any who may benefit less? If so, please describe them and explain why.	I feel that children especially, would benefit from having to have the discomfort of treatment less often. Also patients who live in remote areas or on low incomes may find the reduced frequency of treatment easier to manage, as the cost & time required to maintain

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	hospital visits can be high. (up to £140 a month with parking, fuel & congestion charge costs) Newly diagnosed patients may find the more regular interaction with health care professionals that comes with the Eculizumab schedule, comforting & reassuring in the early months of recovery.
Equality	
12. Are there any potential equality issues that should be taken into account when considering aHUS and treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	From what I understand, onset is more likely to occur in children than adults (60/40) and that in adults, females are affected more often than males, as pregnancy can be a trigger.

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

14a. What are the main benefits of the ravulizumab dosing schedule? 14b. What are the main benefits of ravulizumab for carers? 14c. Are there any other benefits of ravulizumab that have not been captured?	• The positive impact on mental health by allowing patients to feel like they can resume a more "normal life" • The reduced costs of travel • Increased capacity to fulfil work and/or childcare commitments.
15. Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • After living with Covid restrictions for the past year, we all see the immense value we hold for "normal life" and the negative impact on mental health when we are forced to constantly adapt our usual routines. With the current Eculizumab shedule being every other week, most decisions in life revolve around being back for treatment i.e. work commitments, weekend plans,	

holidays etc. Even after nearly 5 years of this constant need to adapt life around treatment, it has not felt any more normal and still very disruptive. Ravulizumab is a huge positive step forward for patients with aHUS returning to a more “normal life”.

- Reducing the overall time spent receiving treatment for aHUS I believe would have a huge positive impact on the confidence and mental health of patients receiving long term treatment.
- Financially, by moving to the treatment schedule that comes with Ravulizumab, the reduced cost of travel and additional capacity to earn will be of great benefit to all patients living with aHUS

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 11 February 2021**

NICE National Institute for Health and Care Excellence

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with aHUS and current treatment options	
About you	
1. Your name	**David Kavanagh**
2. Name of organisation	**Royal College of Physicians** **National Renal Complement Therapeutics Centre**
3. Job title or position	**Professor of Complement Therapeutics** **Honorary Consultant Nephrologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with aHUS? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	DK has received honoraria for consultancy work from Alexion Pharmaceuticals. DK is a director of and scientific advisor to Gyroscope Therapeutics. DK received advisory board payments from Idorsia, Novartis, ChemoCentryx, Apellis, Biomarin and Sarepta. DK's spouse works for GSK
The aim of treatment for aHUS	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to prevent end stage renal failure and death. A very effect treatment for aHUS already exists in the form of Eculizumab. The main aim of Ravulizumab is only to extend the intervals between dosing.
9. What do you consider a clinically significant treatment	The most important clinical response is patients requiring dialysis at endpoint

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in aHUS?	No. There is no unmet need. There is a highly effective treatment currently available in the form of Eculizumab. The current treatment under review, Ravulizumab, only offers longer dosing intervals.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Currently atypical haemolytic uraemic syndrome is treated with Eculizumab through the single expert centre, the National Renal Complement Therapeutics Centre (https://www.atypicalhus.co.uk/) as per previous NICE guidance. Highly specialised technologies guidance [HST1]Published date: 28 January 2015 Eculizumab for treating atypical haemolytic uraemic syndrome (https://www.nice.org.uk/guidance/hst1)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidelines for the treatment of atypical haemolytic uraemic syndrome are available on the NRCTC website ((atypicalhus.co.uk). The inclusion & exclusion criteria for treatment of primary aHUS are based on clinical trial (N Engl J Med. 2013;368:2169). The exception to this is to the treatment of aHUS in pregnancy, which was an exclusion criteria in this trial. Subsequent analysis of data from the NRCTC and other European centre has demonstrated the role of complement in pregnancy associated aHUS **(**Clin J Am Soc Nephrol 2017 12:1237) This and additional safety data in pregnancy has allowed its use in pregnancy

	These guidelines reflect the KDIGO (kidney disease improving global outcomes) meeting report Kidney Int 2017;91:539.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Atypical haemolytic uraemic syndrome is treated through an NHSE highly specialised service in keeping with the NICE recommendation for a single expert centre. There is no difference of opinion in treatment.
• What impact would the technology have on the current pathway of care?	Ravulizumab would only be used as a second line agent in the majority of cases. Currently eculizumab may be started before all diagnostic tests are available as earlier treatment results in better outcomes. Frequently eculizumab may be stopped after a single dose. With a shorter half-life Eculizumab is a more appropriate agent to use in this situation (i.e. reduced risk of meningococcal sepsis) Additionally, at initiation of Eculizumab, it is not necessarily clear whether a patient has presented early enough for treatment to work. As such a 3 month treatment course is given to gauge recovery of renal function. If there is no recovery of renal function Eculizumab is stopped. Thus a long acting version of the drug is only likely to be considered if the patient has recovered function. Horizon scanning, the SETSaHUS trial (https://www.atypicalhus.co.uk/clinical-trials/sets-ahus-2/) is likely to readout within the next year or so. The SETSaHUS trial was mandated by NICE Highly specialised technologies guidance [HST1]- “a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.” Preliminary data from this suggests that withdrawal of eculizumab from patients may be safely undertaken. Thus it is likely that most patients will be able to withdraw from eculizumab with ongoing monitoring. Thus many patients who would have benefited from reduced infusion frequency may in the very near future undergo eculizumab

	withdrawal. In those patients who relapse and thus may require ongoing complement inhibition Ravulizumab may be a better option, offering longer dosing frequencies. There may be instances where Ravulizumab may be used first line i.e. where a patient has a known mutation from previous genetic screening and the diagnosis can be confirmed from the outset. These will be in the minority.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As stated above, Ravulizumab is for the most part only likely to be used where the diagnosis is definitively established and long term treatment is deemed necessary.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The therapy should be introduced in the setting of the highly specialised service as is currently the case with Eculizumab (National Renal Complement Therapeutics Centre). It should be noted that there were more deaths in the Ravulizumab clinical trial (n=3) than in all the Eculizumab clinical trials (no deaths). Additionally, more patients ended the clinical trial on dialysis with Ravulizumab than in the Eculizumab trials (2.5x increase). Although not statistically significant the small numbers in the trial meant that there was insufficient power to detect these differences. Thus doubts about efficacy and safety remain (Kidney Int. 2020 97:1106) and, as such, close monitoring of clinical endpoints in comparison to those collected with the current standard of care are critically important. It will be critically important to compare Ravulizumab and Eculizumab in the setting of the underlying genetic cause. The company suggest in their submission that they did not consider genetic variants or autoantibodies to be an

	important prognostic factor. This is demonstrably false. The genotype predicts the outcome of disease. With such rarity (0.4 cases per million population per year) a single centre will have the power to detect differences in outcome compared to current standard of care based on past data categorised by genotype. As a personal view, my interpretation of the differences in Ravulizumab and Eculizumab trials is that the difference in death rate and end stage renal failure was due to a failure to enrol the correct patients into the Ravulizumab trial. I base this assumption on the very low mutation rate in the Ravulizumab trial suggesting that incorrect diagnosis was made with possible consequences on outcome. The company's suggestion that genetic analysis has moved on since the initial trial is correct however this should result in a higher mutation rate rather than a lower mutation rate as seen in the Ravulizumab trial. The failure to enrol the correct patients with a diagnosis of aHUS highlights the benefit of highly specialist services for patient care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The highly specialised service, the national renal complement therapeutics centre, already has in place all the diagnostics, patient education material logistics and clinical staff etc. to oversee the introduction of this technology. Investment would be very minimal e.g. a nurse to oversee transition
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Given the mode of action of the drug, no meaningful clinical benefits would be expected in terms of renal outcome and mortality. Indeed available evidence demonstrated more patients on dialysis and dying in the Ravulizumab trial albeit not statistically in a small trial number compared to the Eculizumab trial. The benefit would be purely decreased infusion frequency
• Do you expect the technology to increase	No

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Decreased infusion frequency may improve quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As described previously, Ravulizumab is most appropriate second line treatment in those patients where the diagnosis of atypical haemolytic uraemic syndrome is confirmed, who respond to Eculizumab therapy and who require ongoing therapy. A small group of patients e.g. a pre-identified mutation may benefit from Ravulizumab first-line. Ravulizumab is unlikely to be used in pregnancy, at least until more data is available. As such pre-pregnancy planning is likely to require a switch to Eculizumab
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or	Ravulizumab is unlikely to be easier or more difficult for healthcare professionals to use than Eculizumab. Ravulizumab would be given less frequently. Practically monitoring of Ravulizumab is likely to necessitate a different assay than is currently routinely used and is likely to require minor assay development.

ease of use or additional tests or monitoring needed.)	
Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The criteria for starting Ravulizumab will be very similar to those used by the national renal complement therapeutics centre for initiation of Eculizumab. I.e. the entry criteria for the Eculizumab in aHUS trials (N Engl J Med. 2013;368:2169) plus pregnancy associated aHUS. Ravulizumab will however be used as a second line agent only when Eculizumab is shown to be effective, the diagnosis of aHUS is secure and longer term treatment deemed necessary.
Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Ravulizumab is only a minor modification of the previous medication Eculizumab. The only difference is a slightly longer dosing interval.

• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ravulizumab appears to have largely the same side effect profile as a currently available therapy Eculizumab. I.e. increased risk of infection with encapsulated bacteria. This is currently managed by antibiotic prophylaxis and vaccination. This is the same for both therapies. The trend towards increased mortality and dialysis requiring renal failure in patients treated with Ravulizumab compared to previous clinical trials of Eculizumab will require careful post marketing surveillance.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trial broadly reflects UK practice. The mutation rate in the trial was very low compared to that seen in clinical practice in the UK at the national renal complement therapeutics centre. This suggests that many patients without atypical haemolytic uraemic syndrome were enrolled in the study.
• If not, how could the results be extrapolated to the UK setting?	Although the submission suggests that the genetic predisposition does not influence disease outcome this is demonstrably false. The genetic defect will predict disease outcome and by assessing the clinical trial by mutation type against UK data by genotype it may be possible to compare outcomes in the UK with Eculizumab to the

	Ravulizumab trial. The low number of mutations and autoantibodies to factor H in the Ravulizumab trial may however preclude robust analysis and post authorisation analysis is likely to be required.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes in the trial are mortality and dialysis requiring renal failure at the end of the trial. These were measured however there was not a comparator study arm. As such the comparator was historical data. The numbers of patients in these trials precluded robust analysis. For death and dialysis requiring renal failure the trend favoured the standard of care over Ravulizumab.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator	Unpublished data from the national renal complement therapeutics centre could be sought to compare outcomes with Ravulizumab

treatment(s) since the publication of NICE HST1?	
23. How do data on real-world experience compare with the trial data?	The low mutation rate in the Ravulizumab trial does not compare with real-world data in the United Kingdom. Mutation rate would be far higher. As such the Ravulizumab trial likely contains many patients who did not have atypical haemolytic uraemic syndrome. As such comparison of the trial data with real-world data at the national renal complement therapeutic centre is difficult
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Generalisability of the ravulizumab trials to NHS practice	Although the inclusion criteria and the Ravulizumab trial was broadly similar to that used at the national renal complement therapeutics centre in the UK, it is clear that there were large differences in interpretation of these criteria in the clinical trial. This is witnessed by the very low mutation and autoantibody rate compared to seen in the UK. Granular data on the patients who died are available in the published manuscripts. Careful review of these patients highly suggest that they do not appear to have atypical haemolytic uraemic syndrome.
Relative efficacy of ravulizumab versus eculizumab	It is very difficult to assess relative efficacy of Ravulizumab versus Eculizumab. Randomised trials of Ravulizumab versus Eculizumab are not performed. The comparator were the initial trials of Eculizumab. With the numbers enrolled in the study small, statistically different outcomes would be very difficult to establish. It should be noted that three patients that received Ravulizumab in the clinical trial died and more patients ended the trials on dialysis in the Ravulizumab trial. As such the introduction of Ravulizumab will require careful monitoring versus the historical cohorts of Eculizumab treatment for atypical haemolytic uraemic syndrome in the UK.

Long-term efficacy and safety of ravulizumab	There is little long-term efficacy and safety data from Ravulizumab in atypical HUS.
Relapse rate following treatment discontinuation	Relapse rate following discontinuation will be no different to Eculizumab. It will likely be determined by the underlying genetic predisposition. As an estimate, individuals with mutations in complement genes will have a 50% relapse rate. The relapse rate in individuals with no identified complement mutation is likely to be close to zero
Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations	The SETSaHUS trial (https://www.atypicalhus.co.uk/clinical-trials/sets-ahus-2/) is likely to readout within the next year or so. The STESaHUS trial was mandated by NICE Highly specialised technologies guidance [HST1]- "a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur." Preliminary data from this suggests that withdrawal of eculizumab from patients may be safely undertaken. Thus it is likely that most patients will be able to withdraw from eculizumab with ongoing monitoring. A proportion will relapse requiring longer term treatment.
Treatment discontinuation due to renal response	A proportion of patients with atypical haemolytic uraemic syndrome present too late for the treatment with either Eculizumab or Ravulizumab to be effective. One would predict that there would be no difference in the level of response. These figures are available in the annual report of the national renal complement therapeutics centre. It is likely that Ravulizumab will be used as a second line agent were the diagnosis is confirmed and the response to Eculizumab has already been established. As such treatment discontinuation with Ravulizumab due to failure to respond is unlikely to be an issue.
The submission does not consider the potential use of	

eculizumab biosimilar treatments that may become available in the future.	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- A very effective treatment for atypical haemolytic uraemic syndrome is currently available in the form of Eculizumab with Ravulizumab only offering slightly longer dosing intervals
- Comparison of small single arm trials of Ravulizumab and Eculizumab show nonsignificant trends towards increased mortality and end stage renal failure with Ravulizumab
- Ravulizumab introduction would require careful surveillance to ensure efficacy and safety compared to current Eculizumab use in the NHS
- It is likely that with results of clinical trials of disease driven treatment versus continuous treatment (SETSaHUS), Eculizumab will be withdrawn in the majority of patients resulting in alteration of the current treatment model of life long treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Clinical expert statement & technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 11 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with aHUS and current treatment options	
About you	
1. Your name	**Edwin Wong**
2. Name of organisation	**National Renal Complement Therapeutics Centre**
3. Job title or position	**Consultant Nephrologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with aHUS? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (~~they didn't submit one,~~ I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for aHUS	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Untreated, aHUS will progress to end-stage kidney disease in up to 80% of patients within 1 year and may recur, leading to graft loss in a similar proportion. The main aim of treatment of aHUS is to prevent end-stage kidney disease and recurrence.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	In acute presentation of aHUS, there is ongoing haemolysis, thrombocytopenia and acute kidney injury. I would consider cessation of haemolysis, normalisation of platelet count and improvement in kidney function (as measured by a fall in serum creatinine) as a clinically significant treatment response. This ultimately prevents patients needing long-term dialysis or transplantation therefore improving morbidity and mortality of patients with aHUS.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in aHUS?	Eculizumab is currently available as an effective treatment for the treatment of aHUS. It's current license states lifelong treatment for patients with aHUS and a requirement for long-term fortnightly infusions via an intravenous route. Reduction of fortnightly intravenous infusions is an ongoing unmet need whilst ensuring no additional risk of progression to end-stage kidney disease or disease recurrence occurs.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Eculizumab as per HST1 published 28th January 2015.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines for treatment for aHUS are summarised in Goodship et al, Kidney International (2017).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined in England, and is centralised via a referral pathway to the National aHUS Service, part of the National Renal Complement Therapeutics Centre. Cases of suspected aHUS are referred to the National aHUS Service for consideration of diagnosis and treatment. Treatment with eculizumab is commenced when there is sufficient evidence to support a likely diagnosis of aHUS and if key differential diagnoses have been suitably considered / excluded, notably thrombocytopenic purpura. Treatment with eculizumab is administered on a shared care basis between a local referring team and the National aHUS Service. The clinical diagnosis is continually reviewed based on results of clinical investigations, clinical response to eculizumab and results of complement testing. Patients with a confirmed diagnosis of aHUS remain on long-term treatment as summarised in clinical guidelines and product license.

	The optimal duration of treatment remains an area of debate. An approach of treatment withdrawal and monitoring is currently being studied in a clinical trial (SETS-aHUS). Patients who have end-stage kidney disease due to aHUS may be at risk of disease recurrence. Eculizumab can be approved for use at time of transplant in those with high risk to pre-empt recurrent disease, or reactively in those with lower risk. Risk factors for recurrence (notably complement genetic mutations and/or autoantibodies) are reviewed as part of referrals to the NRCTC for consideration of eculizumab at time of transplantation.
• What impact would the technology have on the current pathway of care?	The proposed technology would not impact current pathway – cases of (suspected) aHUS will be reviewed in the same manner.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Most cases referred to NRCTC are of incident patients with suspected aHUS at time of presentation rather than confirmed aHUS at time of relapse / disease recurrence. Eculizumab is likely to remain the initial treatment for aHUS, especially in incident cases where the diagnosis of aHUS under review. Ravulizumab could be considered in incident patients where the diagnosis of aHUS is confirmed (usually no earlier than ~ 3 months following initial referral) or in prevalent patients with aHUS with relapse / recurrence, if long-term treatment is still considered appropriate.
• How does healthcare resource use differ between the technology and current care?	The interval between infusions would increase from 2 weeks to 8 weeks (or 4 weeks if under 20kg). Impact on healthcare resource depends on where patients currently receive their eculizumab infusions (hospital vs community [such as homecare providers].
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Local teams supervising treatment of patients with aHUS may be secondary care (adults) or tertiary paediatric care. These are mostly nephrology centres, some might be haematology centres. These will be under shared care with the National Service – location of infusions may be hospital vs community [such as homecare providers].
• What investment is needed to introduce the	All existing patients with aHUS currently receiving eculizumab would require review to determine / discuss suitability for switch to ravulizumab.

technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Patients may have improved quality of life due to increased time between infusions.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None known to me at this time.
The use of the technology	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Less frequent infusions – fewer cannulas.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current use of eculizumab mandates a diagnosis of aHUS to inform a decision to continue prolonged treatment; there is no current recommendation to stop treatment in patients with confirmed aHUS. Ravulizumab will be similar, except that it won't be started in incident patients where a diagnosis of aHUS is less certain. Rules for stopping treatment may be introduced if a strategy for discontinuation of eculizumab, monitoring and restarting can be recommended based on available and emerging data.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	No

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Potential to benefit in terms of quality of life, but not in terms of preventing end-stage kidney disease / recurrence following transplant.
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	The technology addresses the current unmet need of requiring long-term fortnightly infusions by reduction in frequency of infusions.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ravulizumab, like eculizumab would carry the burden of risk of meningitis. Patients would require up to date vaccination and long-term antibiotics to reduce risk as well vigilance whilst on treatment. The period of antibiotic use and patient vigilance would be required for many months if ravulizumab has stopped, compared to week (~ 8) if eculizumab is stopped.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Adult patients in trial had a lower rate of mutations (20.5%) compared to current data with a confirmed diagnosis of aHUS in UK clinical practice (60-70%, aHUS Annual Report). This may reflect entry into clinical trial with a wide differential diagnosis and patients that would not have been diagnosed with aHUS in UK clinical practice. In contrast, paediatric patients had a higher mutation rate (90%), and may reflect better a group of patients with aHUS as diagnosed in UK clinical practice. The differential diagnosis in this cohort is narrow, compared to adult counterparts. This may in part explain some of the lower response rates in the adult trial (Rondeau et al, Kidney International 2020). One other trial (Tanaka et al, Paediatric Nephrology 2021) enrolled 10 paediatric patients on eculizumab who switched to ravulizumab – a treatment strategy in clinical practice could be considered but is not a current practice in the UK.
• If not, how could the results be extrapolated to the UK setting?	Variations noted above and below.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Complete TMA response that includes normalisation of platelets, improvement in renal function in addition to death. These were all measured in trials. Response rates in paediatrics (Ariceta et al, Kidney International 2020) were high, 77.7% complete TMA response at 26 weeks / 94.4% complete TMA response at 50 weeks with no deaths. This compares to lower response rates in adults (Rondeau et al Kidney International 2020), 53.6% complete TMA response at 26 weeks and 4 deaths. The lower response rates in adults may reflect that broader inclusion of patients that might not have had aHUS and would not be considered for long-term treatment with eculizumab / ravulizumab as per current treatment pathways.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE HST1?	There is now increasing data on efficacy, eg in renal transplantation preventing risk of relapse as well as data potentially supporting a time limited treatment with eculizumab. Zuber et al Journal of America Society of Nephrology 2019 report significantly reduced risk of recurrence with longer graft survival with the use of prophylactic eculizumab. Fakhouri et al Blood 2020, suggest a strategy of eculizumab discontinuation in aHUS based on complement genetics is reasonable and safe. A randomised clinical trial of the safety of treatment withdrawal is ongoing in the United Kingdom (SETS-aHUS). Additionally, Rondeau et al, Kidney International Reports 2019, identified no new safety concerns in adult or paediatric eculizumab-treated patients with aHUS from an observational dataset of 5 years of registry enrolment.

23. How do data on real-world experience compare with the trial data?	I am not aware of any significant real-world use of ravulizumab.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Generalisability of the ravulizumab trials to NHS practice	The larger trials (Rondeau et al and Ariceta et al) included eculizumab-naïve patients. In these trials, inclusion / exclusion criteria and diagnosis of aHUS takes place over days whereas in NHS clinical practice, the diagnosis of aHUS is established over months prior to a possible plan to continue a strategy of longer-term treatment with eculizumab (or ravulizumab). In NHS practice, clinical response to eculizumab forms part of the evaluation at time of confirming a diagnosis of eculizumab. As per answer to Q12 above, most patients being considered for ravulizumab will have completed a course of eculizumab. There is a published 'switch' trial (Tanaka et al, 2021) that could reflect future clinical pathways.
Relative efficacy of ravulizumab versus eculizumab	Unlikely to be much difference in actual effect on blocking complement haemolytic activity.
Long-term efficacy and safety of ravulizumab	Requires longer-term follow up and collection of data through a registry such as centralised provision in a national aHUS service.

Relapse rate following treatment discontinuation	This is influenced by underlying disease (and complement genetic or antibody profile) rather than choice of treatment (ie ravulizumab vs eculizumab). Patients receiving ravulizumab will have a high relapse rate by virtue of the predisposition to aHUS, that in turn might mandate long-term treatment with complement inhibition, ravulizumab or otherwise.
Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations	This is possible – with treatment started if initial relapse, an approach currently being studied in SETS-aHUS. However, a strategy of multiple treatment discontinuations (and therefore multiple relapses) unlikely to be tolerated by clinician or patient.
Treatment discontinuation due to renal response	
The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future.	The formulation and dosing of a biosimilar is important here. Consideration of Eculizumab biosimilar may be important – however, same QoL arguments apply as to eculizumab if the biosimilar is given fortnightly.
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Clinical practice identifies patients with confirmed aHUS ie patients that may benefit from long-term treatment with complement inhibition. In this group of patients, ravulizumab may be as effective as eculizumab.
- Treatment with ravulizumab instead of eculizumab does not change underlying risk of disease relapse and rationale for duration of treatment with a complement inhibitor.
- Dosing with ravulizumab instead of eculizumab provides an increase in time between doses (generally 2-weekly to 8-weekly).
- Impact of dosing is likely to be measured in terms of quality of life and healthcare impact.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

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Deadline for comments **5pm on Thursday 11 February**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**aHUS alliance Global Action**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of the ravulizumab trials to NHS practice	NO	Trialists' gender and age mixes could be applicable to UK patients; however Asian and transplant rescue patients are over-represented. UK Asian aHUS patients are more likely to be of Southern Asian descent than South East Asian patients which seems to be the case given the trial recruitment sites. The genetic mix overall does not reflect the considerably higher level of patients with Complement Factor H (CFH) and Complement Factor I (CFI) variants in the UK. However, the general outcomes of those on the children's' trials are better than those in the adult trials, maybe due to "late adult presenters", which reflects practice in the NHS.
Key issue 2: Relative efficacy of ravulizumab versus eculizumab	NO	In the absence of head-to-head data and therefore a need to adjust the results of the relevant ravulizumab and eculizumab trials, overall, the data shows that there is little difference in efficacy between the two technologies. It is also reassuring for its use in UK that ravulizumab results improved when the SE Asian trialists were excluded. .
Key issue 3: Long-term efficacy and safety of ravulizumab	NO	Whilst incomplete TMA response at six months is understandable in some cases the trial results are surprising. Furthermore, the outcomes for some patients at more than a year are disappointing. Either there is an aHUS cohort for which ravulizumab is not effective at controlling complement, or something else,

		unresolved, might be hampering control or that cohort does not have complement mediated aHUS.
Key issue 4: Relapse rate following treatment discontinuation	NO	Although all studies answering this question have not yet been consolidated to determine such a rate, only a small minority, much less than 50%, of deemed low risk patients are relapsing after treatment withdrawal. The deemed high risk would have a higher relapse rate meaning possible life-time treatment for them. More needs to be known about them and their response to different disease triggers. More answers are also needed on predictors of relapse. Overall, 50% of all aHUS patients are likely to not need treatment at some stage.
Key issue 5: Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations.	NO	On demand when needed reduces potential long-term harm. Prophylactic treatment ahead of a kidney transplant prevents the harm that is experienced from rescue therapy. Depending on individuals' genetic risk factor and the disappearance of a transitory trigger, multiple treatment discontinuations which allow sufficient remission time intervals, are a possibility. In the trial five post-partum patients withdrew from treatment but may well be susceptible to a future pregnancy trigger. A further discontinuation of treatment could follow another such onset once pregnancy triggering effects have passed. Discontinuing patients would need assured care pathways back to retreatment, as well as self- monitoring skills and self-awareness for treatment withdrawal to be safe.
Key issue 6: Treatment discontinuation due to renal response	NO	Once chronic end stage kidney failure is determined, a remission from aHUS is possible whilst on long term dialysis. Complement inhibitor treatment would usually not be needed, although there may be some residual TMA.
Key issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future	NO	We are aware of eculizumab biosimilars in the pipeline, but we have no knowledge of their effectiveness nor cost. Evidence about them is scarce.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Technical engagement response form

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Association for Paediatric Nephrology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of the ravulizumab trials to NHS practice	**YES/NO**	Since the ALXN1210-aHUS-311 trial did not recruit participants under the age of 18 years, I am restricting my comments on this issue to the ALXN1210-aHUS-312 trial. Cohort 1 – these 18 patients were eculizumab-naïve. Their age and weight distribution appear in keeping with UK patients presenting with aHUS for the first time. I note that 3 patients <10kg were included but that the marketing authorisation is sought for >10kg patients. The baseline characteristics appear typical of children with aHUS. I note that 10/18 (55%) had a pathogenic complement abnormality, which although slightly lower than UK practice is significantly higher than in the 311 trial and therefore more representative of NHS patients. As noted extensively in the ERG report, this group of children do not represent those who would likely commence ravulizumab treatment in the NHS. Cohort 2 – these 10 children switched from eculizumab to ravulizumab treatment. Only 2 of these children were in the <20kg weight bracket, which is an important boundary for ravulizumab treatment – those <20kg receive more frequent dosing. These children had no signs of active disease at switching. This group of children (though extremely small) is representative of the cohort of children currently stable on eculizumab treatment in the NHS who would potentially switch to ravulizumab treatment.

Key issue 2: Relative efficacy of ravulizumab versus eculizumab	**YES/NO**	Since the ALXN1210-aHUS-311 trial did not recruit participants under the age of 18 years, I am restricting my comments on this issue to the ALXN1210-aHUS-312 trial. I note the results of the indirect comparisons presented between the eculizumab trial and ravulizumab trial in table 11. Cohort 1 - The results in this small group of 18 patients are encouraging. The high proportion who achieved platelet normalisation and LDH normalisation and achieve a complete TMA response mirrors the eculizumab data. The speed of this response (30 days) also reflects what we see with eculizumab in clinical practice (comparative data with eculizumab trial not presented). I note that only 4/6 came off dialysis with ravulizumab, which is lower than I would expect with eculizumab, but we don't have details on the timeliness of treatment in these patients, which is a key determinant of renal response. The indirect comparison shows 12% vs 7% dialysis at end-point for Ravulizumab vs eculizumab. It is difficult to draw conclusions about this from such low numbers. Cohort 2 – There is no direct comparator group for these patients in the eculizumab trials. However, these 10 patients demonstrate stable disease control throughout the study period. Whilst encouraging, this does not necessarily equate with efficacy in all patients, as many patients can withdraw from eculizumab without experiencing relapse. However during the duration of the trial, and using the data from the ERG report regarding relapse after withdrawal, up to 60% (6 patients) might have been expected to relapse. Therefore, with the limitation of very small numbers, there is some evidence in paediatric patients that the relative efficacy of ravulizumab vs eculizumab is similar
Key issue 3: Long-term efficacy and safety of ravulizumab	**YES/NO**	There is no data available to assess this. Since the data presented cover the period up to July 2019, there may be additional data on the medium term safety and efficacy available in due course.

Key issue 4: Relapse rate following treatment discontinuation	**YES/NO**	I have reviewed the evidence presented in Table 13 and the sections of the report considering time-dependent relapse rates. I agree that the constant rate for risk of relapse after discontinuation is not in keeping with the evidence suggesting relapse rates are highest initially and then are considerably reduced. I do not think time-dependent relapse rates should be used.
Key issue 5: Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations.	**YES/NO**	Children diagnosed with aHUS currently have a lifelong treatment journey ahead of them. The use of complement inhibition is a balance of risks between disease control and risk of meningococcal infection. Over a lifetime of complement inhibition, the risk of meningococcal infection is likely to be cumulative. Thus the option to switch to on-demand treatment, providing subsequent evidence becomes available to support this approach, is likely to be attractive for children and young people. I anticipate that this will be the likely direction of travel for complement inhibition in aHUS and it will require evidence to support the early detection of relapse.
Key issue 6: Treatment discontinuation due to renal response	**YES/NO**	Once data from the SETS trial is available, it is likely that some children and parents will want to discontinue eculizumab treatment, even if it has been effective. My answer to key issue 6 also covers this.
Key issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future	**YES/NO**	The use of biosimilars in children is likely to be later than in adults due to lack of safety data. I therefore suspect that eculizumab/ravulizumab use would continue for longer in children after the introduction of biosimilars. If children and families have switched to ravulizumab, I think it would be very difficult for them to switch back to fortnightly treatment with biosimiiars. The switch to ravulizumab may bring increased working-life choices for parents which may then need to be curtailed. Children may have had an indwelling port removed due to the reduced frequency of infusions and it would be difficult to justify re-inserting this.

Additional issues

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Renal Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Generalisability of the ravulizumab trials to NHS practice	The larger trials (Rondeau et al and Ariceta et al) included eculizumab-naïve patients. In these trials, inclusion / exclusion criteria and diagnosis of aHUS takes place over days whereas in NHS clinical practice, the diagnosis of aHUS is established over months prior to a possible plan to continue a strategy of longer-term treatment with eculizumab (or ravulizumab). In NHS practice, clinical response to eculizumab forms part of the evaluation at time of confirming a diagnosis of eculizumab. As per answer to Q12 above, most patients being considered for ravulizumab will have completed a course of eculizumab. There is a published 'switch' trial (Tanaka et al, 2021) that could reflect future clinical pathways.
Relative efficacy of ravulizumab versus eculizumab	Unlikely to be much difference in actual effect on blocking complement haemolytic activity.

Long-term efficacy and safety of ravulizumab	Requires longer-term follow up and collection of data through a registry such as centralised provision in a national aHUS service.
Relapse rate following treatment discontinuation	This is influenced by underlying disease (and complement genetic or antibody profile) rather than choice of treatment (ie ravulizumab vs eculizumab). Patients receiving ravulizumab will have a high relapse rate by virtue of the predisposition to aHUS, that in turn might mandate long-term treatment with complement inhibition, ravulizumab or otherwise.
Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations	This is possible – with treatment started if initial relapse, an approach currently being studied in SETS-aHUS. However, a strategy of multiple treatment discontinuations (and therefore multiple relapses) unlikely to be tolerated by clinician or patient.
Treatment discontinuation due to renal response	
The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future.	The formulation and dosing of a biosimilar is important here. Consideration of Eculizumab biosimilar may be important – however, same QoL arguments apply as to eculizumab if the biosimilar is given fortnightly.

Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

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- Treatment with ravulizumab instead of eculizumab does not change underlying risk of disease relapse and rationale for duration of treatment with a complement inhibitor.
- Dosing with ravulizumab instead of eculizumab provides an increase in time between doses (generally 2-weekly to 8-weekly).
- Impact of dosing is likely to be measured in terms of quality of life and healthcare impact.
-

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Uk Renal Pharmacy Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

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Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of the ravulizumab trials to NHS practice	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses Applicable and acceptable – difficult to do head to head comparison as very low patient numbers.
Key issue 2: Relative efficacy of ravulizumab versus eculizumab	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Long-term efficacy and safety of ravulizumab	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Relapse rate following treatment discontinuation	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses No comment
Key issue 5: Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations.	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: Treatment	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or

discontinuation due to renal response		analyses
Key issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future	**YES/NO NO**	Please provide your response to this key issue, including any new evidence, data or analyses Biosimilars have been in the pipeline for over 5 years but not yet made it to Uk trial (I'm not aware) or market place. As an orphan drug investment may be restricted or it may be a difficult molecule to produce, as is case of other monoclonals – basiliximab in transplantation. Awaiting a biosimilar could be a long wait so it is not surprising it is not included in the submission. There could be a long wait for biosimilar. A biosimilar with equivalent efficacy data would be a therapeutic option but it would still restrict patients to dosing every 2 weeks.

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Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Evidence Review Group's Critique of the Company's Response to the Technical Engagement Process

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID1530]

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Date completed 24/02/2021

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE ISSUES RAISED AT TECHNICAL ENGAGEMENT

A number of key issues were raised by the ERG in its appraisal report, which were discussed at technical engagement. These relate to:

Issue 1: Generalisability of the ravulizumab trials to NHS practice;

Issue 2: Relative efficacy of ravulizumab versus eculizumab;

Issue 3: Long-term safety and efficacy of ravulizumab;

Issue 4: Relapse rate following treatment discontinuation;

Issue 5: Possibility of providing treatment 'on demand' and allowing for multiple treatment discontinuations;

Issue 6: Treatment discontinuation due to renal response;

Issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future.

The company provides commentary on each of these issues in their response document to technical engagement. The ERG provides a critical evaluation of the company response below. The company provides additional data in response to two of the key issues: issue 2 on the relative efficacy of ravulizumab and eculizumab, and issue 4 on the relapse rate following treatment discontinuation. The company have shared additional confidential data (1, 2) which they indicate provides support to key issue 3 on the long-term safety and efficacy of ravulizumab.

The company has also confirmed an increased PAS discount that has been offered to NHS England on the list price of ravulizumab. The original PAS price of £[redacted] per 300mg of ravulizumab (representing a discount of [redacted]% on the list price) as used in the company's original base-case analysis has been reduced to £[redacted], representing a further discount of [redacted]% on the list price. The impact of this increased PAS discount on the cost-effectiveness results for ravulizumab on (i) both the company and ERG's preferred analysis; and (ii) ERG scenario analyses and additional company scenarios, has been fully detailed in the company's response to technical engagement. The ERG has validated the company's cost-effectiveness results but has not performed any new analyses because the company has fully presented the results in detail.

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE ISSUES RAISED AT TECHNICAL ENGAGEMENT

2.1 Issue 1: Generalisability of the ravulizumab trials to NHS practice

The ERG disagrees with the company that the ALXN1210-aHUS-311 and ALXN1210-aHUS-312 trials are representative of NHS practice and reflect both treatment-naïve and eculizumab-responsive aHUS patients. As stated in the ERG report (see Sections 3.2.1 and 3.2.2), all of the trial evidence in adults and most of the paediatric evidence for ravulizumab is in eculizumab-naïve patients. Clinical advice to the ERG indicates that for the most part ravulizumab is only likely to be used where the diagnosis is definitively established, if the patient has recovered function following first-line eculizumab treatment and long term treatment is deemed necessary.

The reported mutation rate of patients included in trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312, was described in the clinical expert statement and technical engagement response from 11/02/201 as "very low compared to that seen in clinical practice in the UK at the national renal complement therapeutics centre. This suggests that many patients without atypical haemolytic uraemic syndrome were enrolled in the study." This low mutation rate is all the more concerning since, as noted in the clinical expert statement response, developments in genetic analysis since the eculizumab trials (aHUS-C08-002, aHUS-C10-003 and aHUS-C10-004) were conducted should result in higher rate of mutations rather than the lower mutation rate observed in the ravulizumab trials.

The ERG also disagrees with the following company statement: "The fact that clinical advisors to Alexion and the ERG expect ravulizumab to be used primarily in eculizumab-responsive patients also suggests they are comfortable applying the PNH ravulizumab trial data to this patient group." As discussed in the ERG report (pp.35-36, 67 & 69) and following clinical advice, extrapolation of PNH trials findings to aHUS patients is highly uncertain as they are clinically distinct disorders.

2.2 Issue 2: Relative efficacy of ravulizumab versus eculizumab

Clinical response: rates of complement mutation or autoantibodies differ in ravulizumab and eculizumab trials

The ERG report (see section 3.3.1) noted there was potentially important confounding in ITC analyses due to very low complement mutation or autoantibodies rates in ravulizumab (20.5%) patients in ALXN1210-aHUS-311 compared with patients in eculizumab trials (range 49-76%).

The company response pointed out that genetic testing was unavailable for many patients receiving ravulizumab in ALXN1210-aHUS-311 as this was not a requirement of the trial. In response to issue

2, the company contacted study investigators to enquire whether diagnostic genetic testing had been conducted in routine clinical practice and whether results of that testing could be shared. Some additional data were made available for the adult population of the ALXN1210-aHUS-311 trial. The company response stated: "These data show that [redacted] patients ([redacted]% of the trial population) were not tested for complement mutation or autoantibodies at all; [redacted] of [redacted] patients ([redacted]%) who were tested either in the trial or in clinical practice had an identified complement mutation or autoantibodies. [redacted] of these [redacted] patients ([redacted]%) mounted a complete TMA response in the trial. Of the [redacted] patients who had no identified complement mutation or autoantibodies, [redacted] ([redacted]%) mounted a complete TMA response in the trial." The ERG notes when taking into account these new data there are still substantial differences in identified complement mutation or autoantibody rates for the ravulizumab ALXN1210-aHUS-311 trial ([redacted]) and eculizumab trials (range 49-76%).

Clinical response: TMA response rates in patients with and without complement mutation or autoantibodies in ALXN1210-aHUS-311

The company also report new data on TMA response separately for patients with an identified complement mutation or autoantibodies ([redacted]) and for patients where these variants or autoantibodies were not identified ([redacted]). TMA response was much lower for patients who didn't receive any genetic testing ([redacted] responded at 26 weeks, [redacted]; [redacted] further patient responded in the extension phase, [redacted]; no TMA response data were available for 1 patient).

The company conclude from these data: "The similar complete TMA response rates across these groups support the generalisability of trial outcomes to the UK population despite a potential difference in the prevalence of identified complement mutation or autoantibodies."

The ERG disagrees with this conclusion. First, as noted in the clinical expert statement and technical engagement response from Prof David Kavanagh (also a clinical advisor to the ERG):

"Although the submission suggests that the genetic predisposition does not influence disease outcome this is demonstrably false. The genetic defect will predict disease outcome and by assessing the clinical trial by mutation type against UK data by genotype it may be possible to compare outcomes in the UK with Eculizumab to the Ravulizumab trial. The low number of mutations and autoantibodies to factor H in the Ravulizumab trial may however preclude robust analysis and post authorisation analysis is likely to be required."

Although the ERG welcomes new data provided by the company, we consider these findings insufficient to rule out important confounding in the ITC analyses. Substantial differences between ravulizumab and eculizumab trials on a well-established prognostic factor (i.e. complement mutation

or autoantibodies) remains an important limitation for judging the relative efficacy of these treatments.

There are several limitations to the new data reported by the company. First, separate data for patients with and without identified complement mutation or autoantibodies are only provided for the TMA response outcome.

Second, no new analyses matching ravulizumab and eculizumab groups for this prognostic factor are reported by the company.

Third, conclusions on the comparability of outcomes between patients with or without complement mutation or autoantibodies in the ravulizumab (ALXN1210-aHUS-311) trial are highly uncertain because there is no adjustment for other potential prognostic factors such as transplant status, dialysis at baseline, eGFR at baseline, platelet count at baseline.

Fourth, there remains a substantial proportion ([redacted]) of the trial population of the ravulizumab trial (ALXN1210-aHUS-311) who were not tested for complement mutation or autoantibodies. This is particularly important given the small sample size for this trial (56 patients). These missing data are potentially informative as the TMA response rate ([redacted]) is much lower in this group of patients compared with TMA response rates for those with ([redacted]) or without ([redacted]) identified complement mutation or autoantibodies. It is unclear why response rates for these patients appear to differ.

Clinical response: potentially important differences in the ITC analyses

The company technical engagement response also states that the ITC analyses showed "no clear trends favouring one treatment over another".

However, the ERG disagree with this interpretation. The ERG report (see section 3.4.2) pointed out trends favouring eculizumab for key outcomes (such as patients requiring dialysis at endpoint and mortality) in the ITC analyses. Consistent with these conclusions, Prof David Kavanagh's technical engagement response states that the two most important clinical outcomes are patients requiring dialysis at endpoint and mortality. Therefore, these potential differences remain an important source of uncertainty when judging the relative efficacy of ravulizumab and eculizumab.

Economic response

The cost-effectiveness of ravulizumab compared with eculizumab when both treatments are assumed to have differential efficacy was assessed in a scenario analysis. In this scenario, transition probabilities for changes between CKD health states were based on absolute effects observed in single-arm non-randomised eculizumab and ravulizumab trials based on the ITC analysis. In addition,

it is worth noting that this scenario only captures differences between treatments in one outcome, i.e. CKD stage. An additional utility increment of 0.013 QALYs was also added to ravulizumab to reflect reduced frequency of regular infusions with ravulizumab compared with eculizumab. This increment was informed by a Discrete Choice Experiment (DCE) conducted by the company. The ERG was unclear whether it was appropriate to consider this additional increment because any potential utility gains associated with ravulizumab may have already been reflected in the EQ-5D data collected in the trials, and the company's mixed effects model for estimating utility values did not find a statistically significant effect on the treatment covariate (see Section 4.2.9 of ERG report). As a result, the ERG presented the company's scenario analysis with and without the additional utility increment associated with reduced frequency of regular infusions for ravulizumab.

The company have provided a revised estimate of the cost-effectiveness of ravulizumab compared with eculizumab when both treatments are assumed to have differential efficacy in a scenario analysis that includes:

(i) The revised PAS discount for ravulizumab;
(ii) The ERG's preferred base-case assumptions that include: time-dependent relapse rates following treatment discontinuation (see Issue 4 below), a range of 50% – 100% duration of treatment over remaining lifetime for patients who relapse and re-initiate on treatment (see Issue 5 below), and adequate renal response as a reason for treatment discontinuation (see Issue 6 below);
(iii) Including and excluding the additional utility increment associated with ravulizumab.

In addition, the company also adjusted the QALYs to reflect the range of 50% – 100% duration of treatment over remaining lifetime for patients who relapse and re-initiate on treatment in response to issue 5 below (noting that the ERG only adjusted the costs in its exploratory analysis of this issue). The approach used by the company seems reasonable. However, it is worth highlighting that this exploratory analysis is only indicative of the direction of effect on cost-effectiveness and does not directly address issue 5, which cannot be resolved in the absence of robust evidence to inform the long-term implications of treatment withdrawal. The results of the company's revised scenario are discussed in Section 4 below.

2.3 Issue 3: Long-term safety and efficacy of ravulizumab

In their response to technical engagement, the company reiterated that no data beyond 52 weeks from the Extension Periods of trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 were available yet. They provided two additional sources of evidence: post-launch Periodic Safety Update Reports

(PSURs) for ravulizumab across various clinical settings from December 2018 to June 2020, including exposure to ravulizumab during post-marketing experience of [redacted] patient-years,(1) and 104 week extension phase data from ALXN1210-PNH-301 and ALXN1210-PNH-302 trials (date of data cut was not reported). None of these data sources were incorporated into the company model.(2) As the PSUR includes post-marketing data from ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, the 104 week extension data from these trials are not discussed further.

The PSUR reported a post-marketing meningococcal rate of [redacted] per 100 patient years. This rate is comparable with post-marketing meningococcal rate for eculizumab ([redacted] per 100 patient-years) and with the clinical development programme of ravulizumab ([redacted] per 100 patient-years, [redacted] patient-years of follow up). A total of [redacted] deaths were reported across the clinical trial programme and post-marketing studies and reports from other solicited sources; two fatal cases were related (related or probable) events of meningococcal sepsis. [redacted] related to the use of ravulizumab have been observed following post-marketing experience with ravulizumab.

Although [redacted] related to ravulizumab were identified post-marketing, the lack of longer-term data on aHUS patients means the long-term efficacy and safety of ravulizumab compared with eculizumab in an aHUS population remains uncertain. The ERG maintains that there is insufficient evidence to support the company model assumption that ravulizumab and eculizumab have equivalent long-term efficacy and safety.

2.4 Issue 4: Relapse rate following treatment discontinuation

An important driver of total costs in the model is the assumption that all patients who relapse after treatment discontinuation, re-initiate treatment and remain on treatment for the remainder of their lifetime. This means that the risk of relapse following treatment discontinuation has important implications for the proportion of patients in the model who are back on lifelong treatment. The ERG noted that in the company's original submission, patients faced a constant risk of relapse throughout their treatment discontinuation period, i.e., the risk of relapse was irrespective of the time since treatment discontinuation (or the reasons for discontinuation). The ERG highlighted that a number of studies that reported relapse rates after discontinuation of eculizumab treatment suggest that the risk of relapse is higher shortly after treatment withdrawal and is significantly lower after approximately one year of sustained disease control (see Section 4.2.3.2 of ERG report). This was also supported by the ERG clinical advisers and in agreement with findings before eculizumab was widely available. The ERG further highlighted that the constant risk of relapse used in the company's model had a number of limitations: (i) it was based on a small sample size of only UK patients from the global aHUS registry (11 out of 26 adult patients and 7 out of 14 children relapsed and re-initiated

eculizumab treatment) and a short follow-up of 3.5-4 years; and (ii) an oversimplifying assumption to derive the estimate by dividing the observed number of patients who relapsed over the follow-up period by the total number of patients, without appropriately using survival analysis to account for censoring. To address these concerns, the ERG firstly suggested that time-to-event analysis should be conducted to appropriately estimate the risk of relapse over time and, secondly, consideration should be given to conducting this analysis using the full cohort of patients in the global aHUS registry to significantly increase the sample size and follow-up time period. The ERG's preferred base case results include time-dependent relapse rates based on conducting time-to-event analysis using evidence from UK patients enrolled in the global aHUS registry only. The ERG did not have access to the full cohort in the global aHUS registry and requested additional analyses or evidence from the full cohort to potentially reduce uncertainty in the estimates of time-dependent relapse rates.

In their response to technical engagement, the company agrees with the ERG that the relapse rate following treatment discontinuation is likely to vary over time and accepts the ERG's preferred approach of applying time-dependent relapse rates in the model. In addition, the company provides the Kaplan-Meier data for time from treatment discontinuation to re-initiation of eculizumab from the full cohort of the global aHUS registry in both adults and children. This consisted of 326 adults and 173 children at risk over a period of nearly 8.5 years. Consistent with the ERG's analysis of the UK data, a statistically significant difference between adults and children in the log-rank test was not identified on probability of relapse. The company fitted standard parametric survival models (exponential, Weibull, generalised gamma, Gompertz, log-normal and log-logistic) to the pooled data for adults and children and presented the corresponding curves giving probability of relapse over time.

The approach used by the company is appropriate. All models show decreasing hazards over time, except the exponential as expected. All the models fitted similarly in the first 5 years but the extrapolated hazards across the fitted models showed some divergence from this point forward, where the number of patients at risk was very limited (less than 9 patients in total) and non-existent beyond 8.5 years. The best model fit based on AIC/BIC values was the generalised gamma and log-normal curves although the difference across the fitted curves was small. The generalised gamma and Gompertz curves result in approximately 10% of patients who will never relapse and re-initiate treatment during their lifetime, which the company indicates is not consistent with clinical opinion.

The predicted relapse rates, per two-week model cycle, over time from the various extrapolation curves based on the full cohort of the global aHUS registry are compared to the predicted rates used in the ERG's preferred base case analysis based only on UK patients in the registry (Figure 1 below). The predicted relapse rates over the long-term based on UK patients only are broadly aligned with the rates based on a substantially larger cohort from the full registry although the risk of relapse is predicted to be generally higher over time for UK patients. In the absence of adequate evidence to

externally validate the plausibility of the estimates from these models, the ERG considers the company's approach to be appropriate, whereby they present the cost-effectiveness results for ravulizumab in a scenario analysis using the alternative long-term extrapolation curves from the full cohort of the global aHUS registry. The company has indicated that their preference is to use the UK registry data, as presented as part of the ERG's preferred base case assumptions, because it believes that the data is more likely to be reflective of UK clinical practice. The ERG accepts this logic but also notes that (i) the sample size from the full cohort registry is over 12 times the size of the sample of UK patients; (ii) the follow-up period is twice as long in the full registry; and (iii) the time-dependent relapse rates from the UK registry provide more favourable cost-effectiveness results for ravulizumab compared to the full registry cohort.

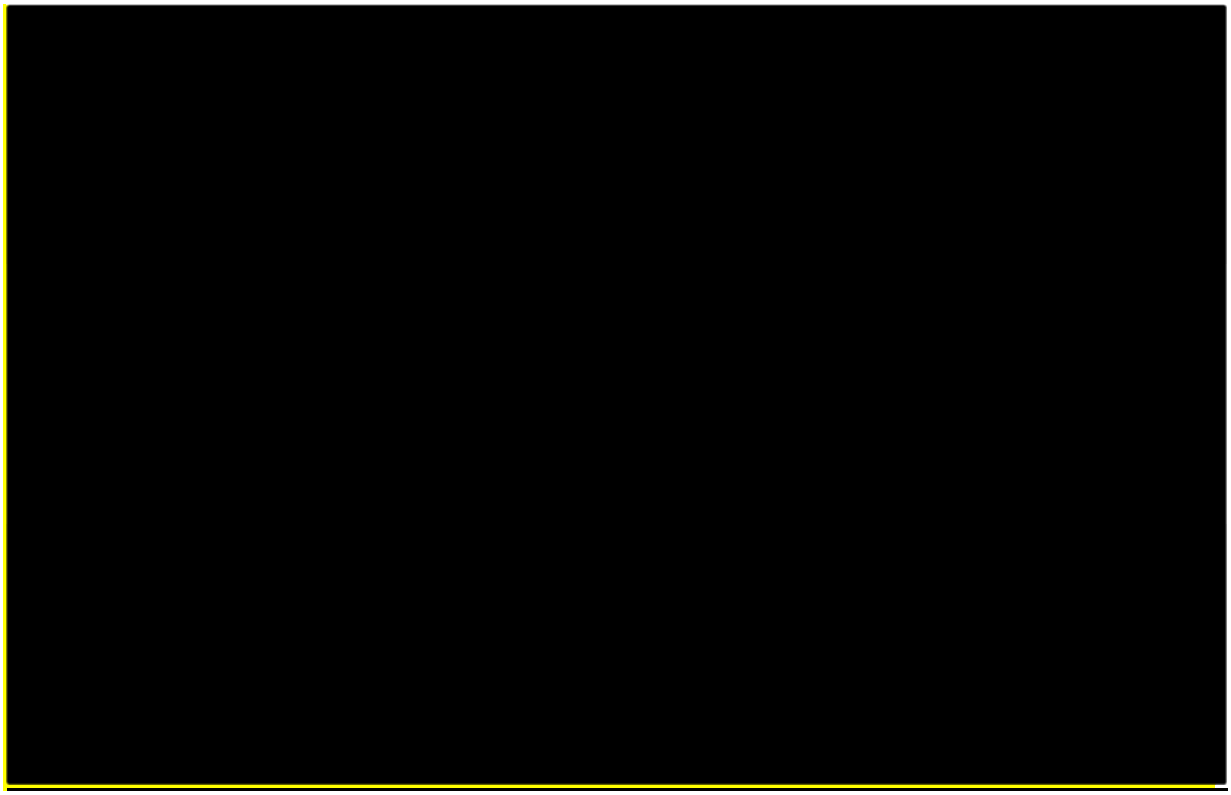

Figure 1 Predicted relapse rates, per two-week model cycle, over time for different parametric models based on the full cohort of patients in the global aHUS registry and dashed line for UK patients only used in the ERG base-case with log-logistic model.

2.5 Issue 5: Possibility of providing treatment 'on demand' and allowing for multiple treatment discontinuations

As noted as part of the previous issue, an important driver of total costs in the model is the assumption that patients who discontinue treatment and their disease subsequently relapses will re-initiate treatment for the remainder of their lifetime, without being permitted to discontinue treatment again. The ERG acknowledged in its report that there is a paucity of evidence for second and subsequent treatment discontinuations, and highlighted that this is an area of considerable uncertainty with high potential impact on incremental costs and cost-effectiveness. The company has not been able to provide any additional data or analyses to support an 'on demand' treatment approach. The ERG agrees with the company that the ongoing Stopping Eculizumab Treatment Safely (SETS) study may provide supportive evidence to assess the safety and impact of eculizumab withdrawal and time to re-initiation of treatment, but it is not designed to assess multiple treatment discontinuations. Therefore, due to a lack of robust evidence, this issue remains unresolved.

In an attempt to reflect the impact on cost-effectiveness of the fact that not all patients who relapse and re-initiate treatment would do so for the remainder of their lifetime, the ERG presented in their preferred base case analysis, a range of results that considered 50 – 100% duration of treatment over remaining lifetime, i.e., for the lower end of the range, patients who relapse receive treatment only for 50% of their remaining lifetime, while for the upper end of the range, patients receive treatment for 100% of their remaining lifetime, which corresponds with the company's base case assumption. It is important, however, to note that this exploratory analysis does not address the issue raised here but only provides an indication that the magnitude of the cost savings associated with ravulizumab compared to eculizumab may not be as large as presented in the company's original submission.

2.6 Issue 6: Treatment discontinuation due to renal response

The ERG noted in its report that the company considered treatment discontinuation due to adequate renal response only in a scenario analysis. As a result, the company's original base case results are based on the assumption that patients discontinue treatment only for reasons related to negative aspects of treatment, i.e. lack of renal response, adverse events or patient preferences, while potential positive aspects of treatment such as its ability to induce renal response and adequately control the disease were not reflected. As stated in the company's response to technical engagement, the ERG was concerned that the number of patients in the model reinitiating on lifelong treatment following disease relapse seemed high (around 50% in the first five years) if discontinuation due to adequate renal response was excluded as a viable reason for discontinuation. This is because it would seem more likely that patients who re-initiate treatment do so because they have evidence that complement-inhibitor treatment adequately controls their disease.

The company's revised base case analysis following technical engagement has accepted the ERG's preferred assumption to include adequate renal response as a reason for treatment discontinuation.

2.7 Issue 7: The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future.

The ERG highlighted the potential use of eculizumab biosimilar treatments that may become available in the future (see Section 4.2.5 of ERG report). The ERG agrees that the only relevant comparator for this appraisal is eculizumab in line with the NICE scope for this appraisal. The ERG has only highlighted the eculizumab biosimilar treatments that are likely to become available in the future because: (i) if an eculizumab biosimilar is offered at an adequate discount, then ravulizumab may not be cost saving in the future; and (ii) if ravulizumab is approved, current practice may switch from eculizumab to ravulizumab making it more challenging in the future for clinicians and patients to potentially switch back to a treatment like eculizumab (eculizumab biosimilar) with increased treatment administration burden compared to ravulizumab. This latter concern was also raised by the British Association for Paediatric Nephrology in its response to technical engagement.

NICE representatives at the technical engagement call indicated that the potential impact of future biosimilars would not be discussed at the committee meeting. Therefore, the ERG accepts the company response that this issue is resolved.

3 CRITIQUE OF THE COMPANY'S PREFERRED BASE-CASE FOLLOWING TECHNICAL ENGAGEMENT

The company submitted a revised base-case following technical engagement. This base-case includes the increased PAS discount of [redacted]% for ravulizumab (total PAS discount of [redacted]% on the list price) and accepts the following ERG's preferred assumptions:

1. Use of time-dependent relapse rates following treatment discontinuation based on data from UK patients only in the global aHUS registry;
2. Includes adequate renal response as a reason for treatment discontinuation.

The company did not show in its revised base-case the implications of a range of 50% – 100% duration of treatment over remaining lifetime for patients who relapse and re-initiate on treatment, i.e., the company's revised base-case corresponds to the assumption that all patients who discontinue treatment and their disease subsequently relapses will re-initiate lifelong treatment (upper 100% end of range). However, the company did present the results of the ERG's preferred analysis with the updated PAS discount that includes the results for the 50% – 100% range of treatment over remaining lifetime.

Table 1 shows the cost-effectiveness results of the company's original and revised base-case analysis, together with the ERG's updated base-case results with the revised PAS. The results indicate that ravulizumab [redacted].

Table 1 Summary deterministic cost-effectiveness results of company's original and revised base-case analysis and ERG's updated base-case with revised PAS.

	Incremental costs for RAV vs. ECU (£)	ICER for RAV vs. ECU
Company's original base-case (with revised PAS)	[redacted]	[redacted]
Company's revised base-case following TE	[redacted]	[redacted]
ERG updated base-case with revised PAS (The presented range corresponds to the range of 50% – 100% duration of treatment over remaining lifetime for patients who relapse and re-initiate on treatment)	[redacted] [redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; RAV, ravulizumab; ECU, eculizumab; TE, technical engagement.

The company also presented results of a scenario analysis using alternative time-dependent relapse rates following treatment discontinuation based on data from the full cohort of the global aHUS registry. Under this scenario, the incremental costs for ravulizumab compared with eculizumab ranged from [redacted] to [redacted], [redacted].

One additional important scenario is when ravulizumab and eculizumab are assumed to have differential efficacy. As noted under issue 2, the company provided a revised estimate of the cost-effectiveness of ravulizumab when both treatments are assessed to have differential efficacy using the ERG's preferred base-case assumptions, including and excluding the additional utility increment for ravulizumab associated with reduced frequency of regular infusions, adjusting the QALYs to reflect the range of 50% – 100% duration of treatment over remaining lifetime for patients who relapse and re-initiate on treatment, and including the revised PAS discount for ravulizumab. Table 2 shows the cost-effectiveness results of the company's scenario analysis with differential efficacy for ravulizumab and eculizumab. This is the only scenario where ravulizumab is [redacted]. It is important to highlight that this analysis is based on the company's ITC analysis which used single-arm eculizumab and ravulizumab studies and compared their absolute effects based on propensity score weighting methods. The ERG highlights that the relative efficacy between ravulizumab and eculizumab is highly uncertain and appropriate evaluation of the relative effectiveness would require randomised evidence, but recognises that this may never become available due to the rare nature of aHUS.

Table 2 Summary deterministic cost-effectiveness results of company's revised scenario analysis for differential efficacy of ravulizumab and eculizumab

	Discounted costs (£)		Discounted QALYs		ICER for RAV vs ECU
Differential efficacy	RAV	ECU	RAV	ECU	
With additional utility increment for RAV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without additional utility increment for RAV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; RAV, ravulizumab; ECU, eculizumab.

[redacted]

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